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DYSOSTOSIS MULTIPLEX (HURLER'S DISEASE; LIPOCHONDRODYSPLASIA; GARGOYLISM)

REPORT OF THE OCULAR FINDINGS IN FIVE CASES, WITH A REVIEW OF THE LITERATURE

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Dysostosis multiplex is a rare disease of congenital origin characterized by chondrodystrophic skeletal changes and deposition of a lipid-like substance in many of the body tissues. The typical picture is that of dwarfism with deformity of the limbs and enlargement of the liver and spleen. The head is large, the orbits widely spread and the root of the nose broad and depressed. The alveolar processes are large and the tongue thick and fleshy. The neck is very short, the spine kyphotic and the belly protuberant. In a majority of the cases there is a corneal haze present. Because of the characteristic large head and grotesque inhuman facies, Ellis, Sheldon and Capon [1] in 1936 suggested the name gargoylism for the disease. Ocular signs are both interesting and diagnostically important in over three fourths of the cases and are important from a prognostic standpoint.

The condition is not mentioned in textbooks on ophthalmology, and therefore a review of the subject is warranted.

HISTORICAL

The first description of the disease in the literature was by Hunter [2] in 1917 in a paper entitled "A Rare Disease Occurring in Two Brothers." In this account he gave a classic description of the disease as seen in 2 brothers, aged 8 and 10 years, who were the only children

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1. Ellis, R. W. B.; Sheldon, W., and Capon, N. B.: Quart. J. Med. **5**:119, 1936.

2. Hunter, C.: Proc. Roy. Soc. Med. **10**:104, 1917.

of healthy parents. No mention was made of ocular involvement. Hurler [3] in 1919 reported 2 cases and first described the disease as a separate entity associated with characteristic corneal cloudiness.

ETIOLOGY

The disease is of congenital origin and, as has been stated by Kressler and Aegerter,[4] is familial in nature. Husler [5] described it as familial and genotypical. Ashby, Stewart and Watkin [6] stated that, while the disease is familial, there is usually no history of a previous occurrence. There is no racial limitation, cases having been reported from many countries. Engel [7] reported the disease in 2 Chinese brothers. Among the cases reported 54 per cent of the patients were male; so the sexes are affected about equally. Also, the disease may involve several members of the family. Including the cases presented here there are 11 instances in which 2 siblings were affected, while in the families reported on by Ruggles,[8] Ellis, Sheldon and Capon [1] and Nonne [9] 3 siblings had the disease. The condition has also been noted in twins. In Nonne's [9] cases twin sisters were affected, while Gasteiger and Liebenam [10] reported an instance in which one twin sister had the disease and the other was free from it. Case 1 in our series was that of a female twin whose sister was unaffected, while in case 4 the male patient had a normal twin sister. From these facts it is apparent that of twins one or both may be affected.

Washington [11] collected 44 cases which had been reported up to the end of 1939. These together with the case reported by Veasey [12] and the 5 cases presented here bring the total to 50.

Ellis, Sheldon and Capon [1] stated that biochemical investigation in their cases revealed nothing definite. Kressler and Aegerter [4] found no evidence of thyroid involvement either clinically or at postmortem examination, and Pfaundler [13] expressed the opinion that there is no evidence of endocrine disturbance. As Washington [11] has pointed out, no known glandular dysfunction produces the characteristic picture.

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3. Hurler, G.: Ztschr. f. Kinderh. **24**:220, 1919.
4. Kressler, R. J., and Aegerter, E.: J. Pediat. **12**:579, 1938.
5. Husler, J., in Pfaundler, M., and Schlossmann, A.: Diseases of Children, translated by M. G. Peterman, Philadelphia, J. B. Lippincott Company, 1935, vol. 2, p. 29.
6. Ashby, W. R.; Stewart, R. M., and Watkin, J. H.: Brain **60**:149, 1937.
7. Engel, D.: Arch. Dis. Childhood **14**:217, 1939.
8. Ruggles, H.: Am. J. Roentgenol. **25**:91, 1931.
9. Nonne, M.: Deutsche Ztschr. f. Nervenh. **83**:263, 1925.
10. Gasteiger, L., and Liebenam, L.: Klin. Monatsbl. f. Augenh. **99**:433, 1937.
11. Washington, J. A., in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1937, vol. 4, chap. 31, p. 1; supp., 1939.
12. Veasey, C. A., Jr.: Ocular Findings Associated with Dysostosis Multiplex and Morquio's Disease: Report of Case of the Former, Arch. Ophth. **25**:557 (April) 1941.
13. Pfaundler, M.: Jahrb. f. Kinderh. **92**:419, 1920.

Consanguinity apparently plays no role in the disease, although in the first case reported by Binswanger and Ullrich[14] the maternal great-grandmother and the paternal grandfather were brother and sister.

Besdziek[15] reported the disease in 2 brothers. In the male line of the family there was a history of broad skulls, the father, his brother and the grandfather each having a skull with a circumference of 61 cm.

SYMPTOMATOLOGY

At birth there are usually no abnormalities, although in several instances enlargement of the head and corneal cloudiness were noted. The first signs usually appear toward the end of the first year of life, when enlargement of the head and dorsolumbar kyphosis make their appearance. The head usually becomes scaphocephalic, with a prominent forehead and supraorbital ridges. At this time failure in normal development is also noted, in that the child does not learn to walk, talk or feed himself. After an initial normal growth, normal development ceases and the child begins to assume the characteristic appearance, with disproportionate dwarfism. As typical of dysostosis multiplex may be mentioned a massive facial portion of the skull, with prominent frontal bosses. The globes are wide set and slightly protuberant, and the root of the nose becomes sunken, producing a saddle nose with flaring nares. Owing to the nasal deformity and to enlarged pharyngeal adenoid tissue the child becomes a mouth breather, which gives him the appearance of having thickened lips. The alveolar processes are large and the tongue thick and fleshy. The neck is so short that the head seems to rest directly on the shoulders. Narrowing and shortening of the rib cage develop, with nodular costochondral junctions and Harrison's groove. A striking finding is the very protuberant abdomen. Umbilical hernia is always present in some degree. On palpation, in nearly every case the liver and spleen have been found to be enlarged.

Probably one of the most diagnostic features of the disease is the development of malformed hands, wrists, elbows and shoulder and hip joints. The hands become broadened, with thick, incurved fingers, and there is slight enlargement in the wrist and the elbow joints, which are limited in their extension. Abduction of the shoulder joints is usually curtailed, and Sprengel's deformity is frequently reported. The lower extremities are usually less affected, but extension of the hips and knees is often diminished. The kyphosis as a rule occurs in the lower part of the thoracic and in the upper part of the lumbar region, is permanent and is unaffected by treatment. The changes are usually accompanied by muscular flaccidity.

As the child approaches the age of 3 or 4, the dwarfing becomes more striking because of failure in growth of the long bones and the

14. Binswanger, E., and Ullrich, O.: Ztschr. f. Kinderh. **54**:699, 1933.
15. Besdziek, I.: Monatschr. f. Kinderh. **76**:305, 1938.

vertebral column. This, together with other changes, gives him a characteristic appearance, which Ellis and his co-workers [1] have described as gargoyle-like, owing to the crouching stance, large head, unusual facies, short neck and protuberant abdomen. Mental retardation may also be present and as the child grows older may become more pronounced because of the progressively poor visual acuity and hearing. In some patients this retardation apparently results from involvement of the central nervous system, as seen at autopsy by Tuthill [16] and Kressler and Aegerter.[4] Other patients, for example Meyer and Okner's [17] 7 year old girl, may have normal mentality.

OCULAR FINDINGS

A distinctive clouding or haziness of the corneas occurs in over 75 per cent of the cases. In some reports no mention is made of the corneas. Cockayne [18] reported a case in which the corneas remained clear, while Hunter's [2] patients, brothers aged 10 and 8, had no corneal involvement. When present clouding is diagnostic of the disease. Washington [11] stated that the prognosis is better in the absence of this clouding. It appeared in 16 cases before the age of 2 years. In 2 instances it was present at birth. In Ashby, Stewart and Watkin's [6] first case corneal cloudiness was noted at birth, while in Ellis, Sheldon and Capon's [1] fourth case the eyes were described as always being cloudy. In most cases the haziness appears before the age of 3 years. It is always bilateral, commencing in the two eyes at the same time and progressing equally in the two eyes.

Examination in the early stages by Ellis and co-workers [1] (case 6) and Berliner [19] showed the opacities to be located in the deeper layers of the corneal stroma. As the disease progresses the opacification becomes more diffuse, involving uniformly all the corneal layers except the epithelium and the endothelium. The earliest slit lamp microscope examination is that of Berliner [19] of a 7 month old child. He noted that the opacification commenced in the central portions, the periphery being clear. It occupied the anterior middle layers and increased in density toward the posterior layers. Slit lamp microscope examination of older children by Meyer and Okner,[17] Bindschedler,[20] Ellis and co-workers [1] and in our cases showed the opacities to be spread diffusely

16. Tuthill, C. R.: Juvenile Amaurotic Idiocy: Marked Adventitial Growth Associated with Skeletal Malformations and Tuberculomas, Arch. Neurol. & Psychiat. **32**:198 (July) 1934.

17. Meyer, S. J., and Okner, H. B.: Am. J. Ophth. **22**:713, 1939.

18. Cockayne, E. A.: Proc. Roy. Soc. Med. **30**:104, 1937.

19. Berliner, M. L.: Lipin Keratosis of Hurler's Syndrome (Gargoylism or Dysostosis Multiplex): Clinical and Pathologic Report, Arch. Ophth. **22**:97 (July) 1939.

20. Bindschedler, J. J.: Bull. Soc. de pédiat. de Paris **36**:571, 1938.

through the corneal stroma. On examination with the slit lamp the opacification is resolved into uniformly distributed tiny gray or yellowish gray dots. In direct illumination their surfaces seem slightly refractile but do not give the appearance of being crystalline. By retroillumination they are seen to be closely packed throughout the stroma and have a dull appearance. Cockayne [21] in 1935 called this opacification a corneal dystrophy.

After its initial appearance, the opacity never disappears and rarely varies in intensity. Bindschedler [20] noted some variation in 1 case.

When fully developed the clouding appears as a uniform, milky haze in diffuse illumination. Ellis [22] said this haze is not unlike that seen in buphthalmos. It is accompanied by no sign of inflammation, and there is no tendency for the cornea to become vascularized. The corneal opacity somewhat resembles interstitial keratitis. In fact, our third case was considered elsewhere as an instance of congenital syphilis, the ocular consultants having diagnosed the corneal condition as interstitial keratitis. The patient was treated six months for syphilis in spite of the fact that repeated Wassermann and Kahn tests of the blood and spinal fluid were negative. The appearance is similar to that seen in acute glaucoma but without the signs of inflammation.

After a certain stage of opacification is reached there does not seem to be further progression. Also, further degenerative changes have not been reported in any of the older patients (15 to 20 years of age).

In the beginning the opacification does not seem to affect the vision, but as it progresses the acuity is decidedly diminished. In most cases it is not possible to determine the vision because of the age of the patient. The visual acuity has, however, been recorded in some instances which illustrate the variation mentioned. In Gasteiger's [10] case the slit lamp disclosed the typical corneal changes but there was 20/20 vision in each eye. In Engel's [7] case the vision was 20/100, while in Berliner's [19] second and third cases the vision was 20/200 and 10/200, respectively. Those corneas which have fairly dense clouding obstruct a view of the iris and the fundus.

It was stated under the heading "Symptomatology" that the globes are practically always set widely apart. Enlargement of the skull and unusual development of the sphenoid bone account for this anomaly.

The lids are usually somewhat thickened and heavy. The globes appear large and somewhat protuberant, though definite exophthalmos has never been reported. It has been stated in a number of cases that the corneas are larger than normal. That this may be so is borne out by the fourth case of Ellis and co-workers,[1] in which the corneas measured 14 mm., as they did in Meyer and Okner's [17] case. The usually accepted average is 11.65 mm. for the adult male cornea and

21. Cockayne, E. A.: Proc. Roy. Soc. Med. **28**:1067, 1935.
22. Ellis, R. W. B.: Proc. Roy. Soc. Med. **31**:770, 1938.

11.54 mm. for the adult female cornea. Gillespie and Siegling [23] mentioned that the corneas appeared larger than normal, but this impression was not confirmed by actual measurement.

The appearance of large globes and hazy corneas would make one think of buphthalmos. In a large number of cases the tension during anesthesia has been found to be normal. In a few instances tonometric readings have been recorded. Berliner [19] found a tension of 14 mm. Schiøtz) in his case. Meyer and Okner [17] found a reading of 25 mm. (Schiøtz-Gradle), while Gillespie and Siegling [23] found an intraocular tension of 25 mm. in the right eye and of 22 mm. in the left. In all of our cases in which the tension was taken with the Schiøtz tonometer it was within normal limits.

Bindschedler [24] found the tension "sometimes elevated, and sometimes normal" in his 2 cases. Anterior sclerotomy was performed in 1 of them and trephining in the other without effect on the corneal clouding but with control of the tension. Davis and Currier [25] found bilateral buphthalmos in 2 brothers. Bilateral iridectomy was performed in 1 of the boys, but the results were not reported. Four years later both patients were seen, and both had bilateral optic nerve atrophy. It was not stated whether this was of a glaucomatous nature. Encephalograms showed hydrocephalus which might have been the cause of the atrophy. Ashby and co-workers [6] mentioned that a moderate increase in tension existed in the terminal stages in their patient. In 1 of our cases (case 2) bilateral trephining had been performed at another institution before we saw the patient, and a letter of inquiry brought the reply that the tension was definitely elevated.

The fundus apparently shows no typical changes and is usually reported as normal. There are a few instances in which fundus changes were recorded. Davis and Currier [25] reported dysostosis multiplex in their 2 cases, in both of which there were buphthalmos and hydrocephalus. In each instance there was bilateral complete optic nerve atrophy. Slot and Burgess [26] stated that in their case the disk was "red, vascular and congested." In case 1 of our series there was a haziness of the disk with edema of 1 to 2 D. Encephalograms showed uniform dilatation of the ventricles, which might have accounted for the changes in the disk.

Convergent squint has been recorded in 3 instances; in one by Putnam and Pelkan,[27] in another by Helmholz and Harrington

23. Gillespie, J. B., and Siegling, J. A.: J. Bone & Joint Surg. **22**:171, 1940.
24. Bindschedler, J. J.; Rodier, J. M., and Heintz-Bertsch (Mme.): Rev. franç. de pédiat. **14**:116, 1938.
25. Davis, D. B., and Currier, F. P.: Morquio's Disease: Report of Two Cases, J. A. M. A. **102**:2173 (June 30) 1934.
26. Slot, G., and Burgess, J. L.: Proc. Roy. Soc. Med. **31**:113, 1938.
27. Putnam, M. C., and Pelkan, K. F.: Scaphocephaly with Malformations of Skeleton and Other Tissues, Am. J. Dis. Child. **29**:51 (Jan.) 1925.

(case 4) [28] and in a third by Bindschedler (case 2).[24] One of our patients (G. N.) also had a convergent squint.

OCULAR PATHOLOGIC CHANGES

Only 2 instances are recorded of microscopic examination of eyes obtained at autopsy.

Kressler and Aegerter [4] examined the eye of a child with cloudy corneas who died at the age of 8½ years. The choroid, retina, iris and lens appeared healthy. The anterior and posterior epithelial layers of the cornea were normal, but the laminas of the cornea proper were widely separated. The authors were not sure whether this was due to infiltration from disease, to edema or to an artefact from fixation.

Berliner,[19] in reviewing the postmortem observations of Kressler and Aegerter,[4] said: "A study of the illustration of the corneal preparation which was shown in their article undoubtedly shows that the large areas of separation of the corneal lamellas were entirely due to artefact."

The second report is that of Berliner,[19] who examined the right eye of a 5 year old boy with cloudy corneas. Pyroxylin sections were prepared with a variety of stains. Gelatin mounts showed no neutral fat. The deeper and central areas of the cornea, corresponding to the infiltrated area, stained lighter than the normal portions. Bowman's membrane was missing in places and was replaced by cells with vacuolated cytoplasm, the cells varying from spindle shaped to globular. The corneal nuclei lay in spindle-shaped vacuolated spaces. In the deeper central regions these vacuolated spaces contained granular staining material. The presence of lipid granules, Berliner stated, refuted any possibility that these spaces were the result of artefacts. He stated that these lipid granules were well brought out with Masson's stain and with hematoxylin and eosin and were similar to those found in other organs. The rest of the eye was normal.

ROENTGENOLOGIC FINDINGS

During the first six months of life there are no abnormal roentgenologic findings. At 6 months there appears a slight broadening of the humerus, radius and ulna, together with beginning kyphosis.

After the first year the typical findings begin to appear.

Skull.—The head is practically always enlarged, with some degree of scaphocephaly most commonly found. A peculiar feature in a large number of cases is the elongation of the sella turcica without a sign of erosion. This is due to maldevelopment of the sphenoid bone rather than to enlargement of the pituitary gland. It also accounts for the hypertelorism.

28. Helmholz, H. F., and Harrington, E. R.: Syndrome Characterized by Congenital Clouding of Cornea and Other Anomalies, Am. J. Dis. Child. **41**:793 (April) 1931.

Vertebrae.—Dorsolumbar kyphosis is present in almost every case owing to flattening and narrowing of the vertebral bodies involved.

Thorax.—The anterior extremities of the ribs are expanded, with flaring of the lower ribs.

Extremities.—The metacarpal and phalangeal bones are shorter and broader than normal and may be irregular. The ends of the shafts of the long bones are irregular and fragmented, particularly the lower ends of the radiuses and ulnas. Coxa valga is frequently seen.

REPORT OF CASES

The cases reported are from the pediatric service of Dr. William A. Reilly at the University of California Hospital.

CASE 1.—G. N. (fig. 1), a girl, was first seen in the University of California Hospital outpatient department in April 1930 at the age of 1 year and 9 months. Thereafter she was seen intermittently until October 1936.

History.—She was a normal, full term twin girl baby. Her twin sister developed without evidence of the disease. There was no history of any familial disease, and the parents were unrelated. The first symptoms of dysostosis multiplex appeared at about the age of 6 months, when she was treated for dorsolumbar kyphosis. A little later lack of development became apparent with her inability to stand and walk at the usual age. At 20 months she could not walk, talk or feed herself and seemed somewhat dwarfed. The head was abnormally large for her age. Enlargement of the liver and spleen was also noticed. Corneal cloudiness developed at about the age of 3 years, and the eyes were seen to be wide set and apparently somewhat larger than normal.

At the age of 4 years the unusual nature of the disease was recognized and the patient was hospitalized for study. At this time the typical picture of dysostosis multiplex was described though not recognized. Examination of the eyes showed the globes to be wide set, the interpupillary distance measuring 64 mm. There was a fine diffuse clouding of the corneas, so that the fundus details were hazy.

An alternating convergent squint was present.

Encephalograms showed uniform dilatation of the ventricles.

The child was next seen in October 1936, at the age of 8 years and 2 months. At this time she was 36 inches (91 cm.) tall. The twin sister was normal in size and appearance.

Examination.—The head was large, with occipitoparietal flattening. The facies was dull and stupid. The orbits were wide set, with the eyes appearing to be lateral rather than forward. The nose was saddle shaped, with wide nares, and there was an apparent nasal obstruction. The mandible was smaller than normal and was misshapen owing to the absence of condyles. The teeth were peg shaped and asymmetric in size and shape. The hearing seemed to be unimpaired. Sprengel's deformity of the scapulas was present. There were thoracolumbar kyphosis and lumbar scoliosis to the left together with hypertrichosis of the back. The hands were small and stubby, and the phalanges could not be extended. There was a flaring of the ribs. The abdomen was prominent, and there was an umbilical hernia. The liver and the spleen were both enlarged. The patient was unable to stand unassisted and could only mutter inarticulate sounds.

Laboratory examination showed granules in the neutrophils. The dextrose tolerance was normal. Chemical examination of the blood showed 12 mg. of cal-

cium, 4.1 mg. of phosphorus and 93.9 mg. of cholesterol per hundred cubic centimeters. A Wassermann test of the spinal fluid was negative.

The hat band measured 47 cm., the chest 53 cm., the abdomen 55 cm., and the height 90 cm. The weight was 13.4 Kg.

Ocular Examination: The orbits, as previously noted, were widely spread, and the eyes seemed a little more protuberant than formerly. The lids and conjunctivas were not remarkable. An alternating convergent squint was present, although the child fixed primarily with the right eye. The vision seemed poor and could not be accurately determined.

In the right eye fine diffuse clouding was present over the entire cornea; no scars were visible. Details of the iris were seen sufficiently well to reveal that there was no gross pathologic change. The fundus was seen with difficulty and showed some blurring of the disk margins with apparent elevation of the disk; no hemorrhage or exudate was seen.

In the left eye there was corneal cloudiness similar to that in the right eye, but it was more pronounced, so that the fundus was not visible.

Fig. 1 (case 1).—The only available photographs, showing the large head, prominent frontal protuberance, wide set eyes and saddle nose with flaring nares; age, 2 years and 3 months.

Slit lamp examination was not made.

The intraocular tension during anesthesia was 22 in the right eye and 26 in the left eye (Schiøtz).

Roentgenologic Examination: The findings are from the report of Dr. Robert Stone, of the department of roentgenology.

The head was large for the age of the child and showed numerous convolutional markings on the inner table. The lower portions of the coronal sutures were in evidence, but the sagittal suture and the lambdoidal sutures were barely detectable. There was practically no sphenoid bone present, with the result that the sella turcica was placed low, on a level with the floor of the middle fossa. The inferior fossae in the occipital bone were very prominent.

The mandible was shorter than the maxilla; so the upper teeth protruded considerably. The long bones showed extreme irregularity in development, in particular the metacarpal bones and the phalanges; the radiuses and ulnas showed a broadening of the shafts with dwarfing of the epiphysial centers. There was uneven growth in the ends. The lower extremities did not show this to such

an extent. There were coxa valga of the necks of the femurs and poor development of the acetabulums. The ribs had narrow roots and broad bodies. The necks appeared distorted. The spinal canal appeared to be greatly enlarged by an elon-

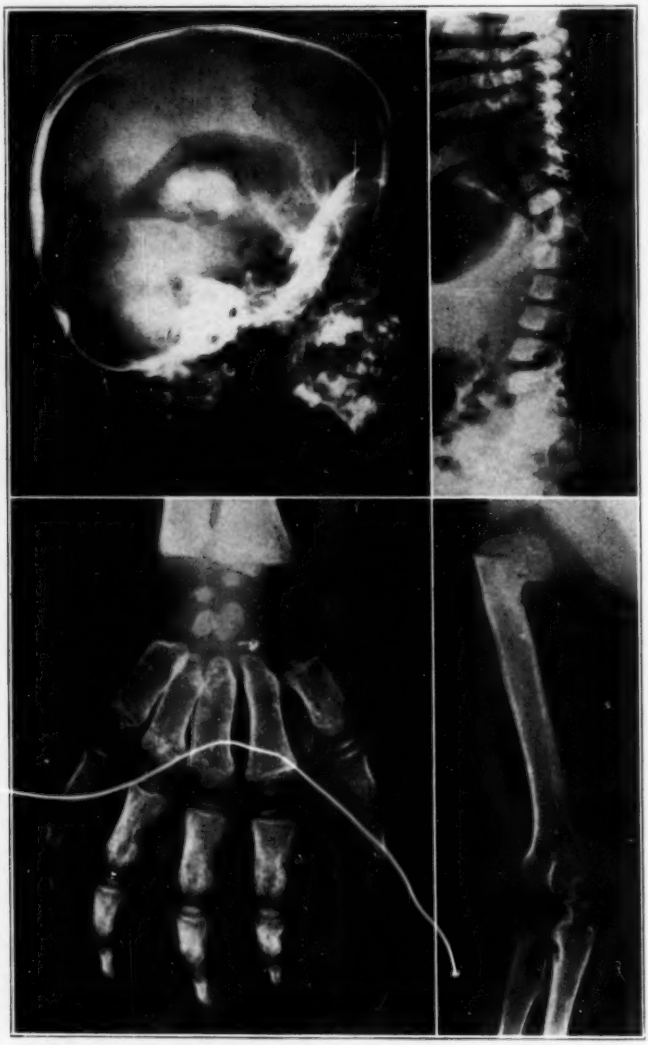

Fig. 2 (case 1).—The principal bony changes seen on roentgen examination.

gation of the vertebral arches in the anterior-posterior direction and by concavities on the posterior surface of the bodies, especially in the lumbar region.

There were also concavities on the anterior surface of the bodies in the lumbar region. In the cervical region there was marked irregularity in the size and the development of the vertebrae (fig. 2).

The findings were classified as those of dyschondroplasia.

Course.—A short time after the child was last seen she was placed in a state home, where she died a few months later. Detailed postmortem observations were not available.

CASE 2.—E. N. (fig. 3), a girl born Aug. 16, 1934, was seen in the University of California Hospital in April 1935 because of an acute infection of the upper respiratory tract.

History.—A younger sister of patient 1 (born six years later), she had had a normal birth at full term and had developed normally until about 8 months of age. At the time of her admission she had some of the stigmas of dysostosis multiplex. The head was large and wide, with widely set eyes; the nose was flat,

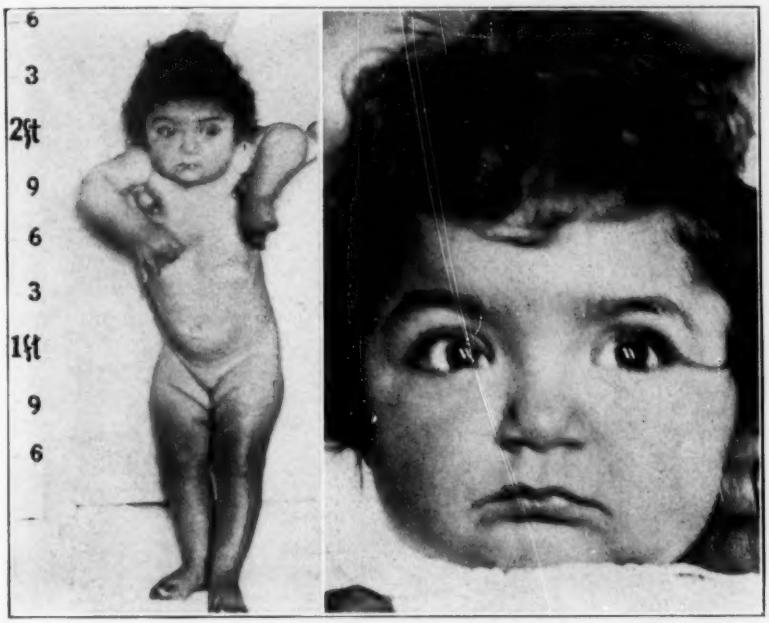

Fig. 3 (case 2).—Typical early changes; age, 2 years and 6 months.

and the abdomen was protuberant, with an enlarged liver and spleen. The corneas were cloudy.

By the time the patient was 1½ years of age it was seen that she was developing in a manner similar to that of her older sister. She was dwarfed and walked with a waddling gait. There was limited extension of the fingers and wrists. The corneas were cloudy.

Examination.—The patient was readmitted to the hospital for study in July 1939, at the age of almost 5 years. At this time a typical picture of dysostosis multiplex was presented. The patient was 37 inches (94 cm.) tall; her head was large and scaphocephalic, with prominent frontal protuberances. The globes seemed enlarged and wide set, with cloudy corneas. A saddle nose and flaring nares made breathing difficult; so the patient was a mouth breather. The neck was so short as to appear to be absent. The abdomen was protuberant, with an umbilical hernia and enlargement of the liver and spleen. In addition, the patient had stiffness of the joints with limited extension (fig. 4).

Fig. 4 (case 2).—The typical picture of dysostosis multiplex; age, 5 years.

Fig. 5 (case 2).—Mild exophthalmos, with haziness of the corneas.

The patient understood conversation but was quiet and inactive. She had a mental age of about 3 years and 5 months, with an intelligence quotient of 69, and was classed as a high grade moron.

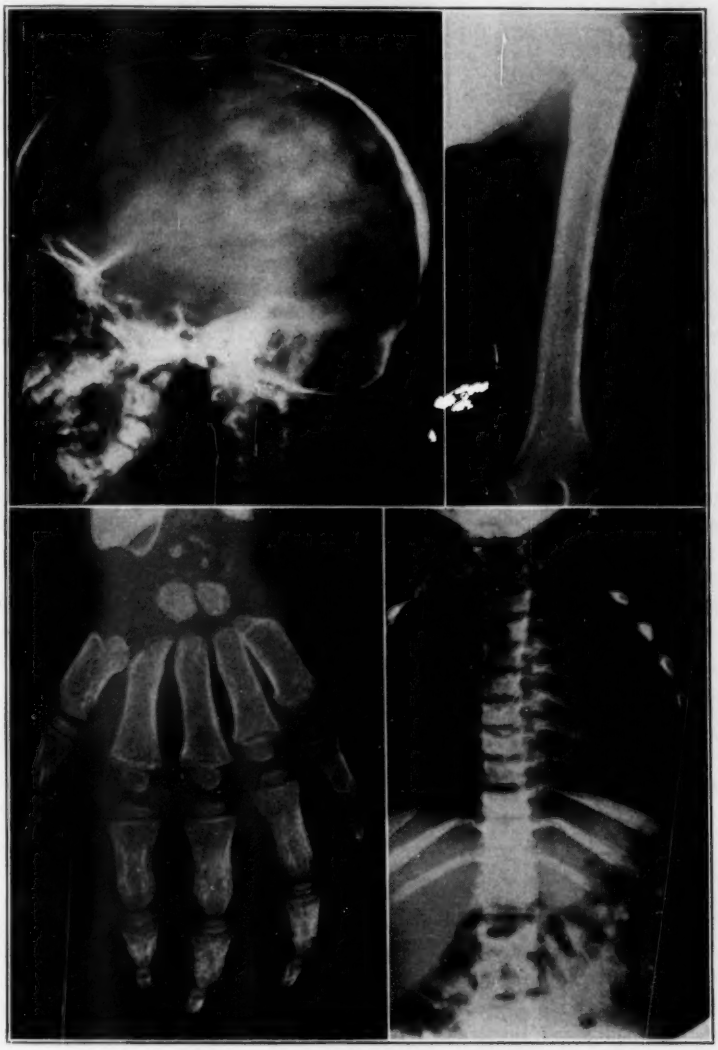

Fig. 6 (case 2).—The roentgen findings.

Ocular Examination: The eyes appeared to be mildly exophthalmic; the upper lids were thickened and somewhat heavy (fig. 5).

The right cornea was diffusely cloudy and appeared to be definitely larger than normal. With oblique illumination it had a gray, milky appearance. During anesthesia the fundus was seen indistinctly and appeared to be normal.

The left cornea was diffusely cloudy, like the right, but to a greater extent, so that the fundus was not visible. At the upper border of the limbus was a small pigmented area, where it was said a trephining had been done several months earlier.

The intraocular tension, taken during anesthesia, was 29 in the right eye and 25 in the left eye (Schiøtz).

Slit lamp examination revealed a flat and regular epithelial layer without abnormality. The endothelium was also normal. Scattered throughout the corneal stroma were small punctate dots that were gray with a suggestion of yellow in the deeper layers. These dots became more numerous and larger in the posterior layers. In some areas there were medium-sized, irregular plaques of denser gray. No evidence of vascularization of the cornea was seen. A few dotlike pigment spots were noted on the anterior surface of the lens.

Laboratory Examination: The white blood cells were granular, and there was a huge percentage of lymphocytes. Biopsies of bone marrow disclosed an extremely high incidence of basophils. The bleeding time was four minutes and the clotting time six minutes.

Roentgenologic Examination: The report, made by Dr. Robert Stone, was almost identical with that on her sister. Dr. Stone stated: "This child has the same type of maldevelopment as her sister" (fig. 6).

Course.—This patient continues under observation in the outpatient department.

Case 3.—J. M. (fig. 7), a girl born March 6, 1931, was seen at the University of California Hospital on Jan. 29, 1940, at the age of 8 years. She had been referred for general examination.

History.—The family history revealed nothing significant. The parents were unrelated.

The child had had repeated attacks of nasopharyngitis and otitis media since the age of 8 months, with resultant diminution of hearing.

The first signs of dysostosis multiplex appeared at 1 year, when she started walking with a waddling gait, the hips and legs being held rigid. Later the fingers became stiffened, and the stiffness spread to the wrists, elbows and shoulders. At the age of 2 years corneal clouding was noted and the condition was diagnosed as interstitial keratitis by an ophthalmologist. A letter from the child's pediatrician in the Middle West stated that she was treated with acetarsone for six months in spite of negative Wassermann and Kahn tests of the blood and spinal fluid.

The child complained frequently of bony pain.

Examination.—The height was 38½ inches (98 cm.). The head was larger than normal and scaphocephalic, with fairly large frontal bosses. The eyes were wide set, with large cloudy corneas. The nose was a typical saddle nose (fig. 8). The patient had thick lips and a thick protruding tongue and was a mouth breather. The teeth were peg shaped and widely spaced. The neck was so short that the head seemed to rest directly on the shoulders. The abdomen was protuberant, with an enlarged liver and spleen. There was a fairly large umbilical hernia. The hands were spatulate, with broad fingers and palms, and there was limitation of motion of all the fingers and of the wrists. The lower ends of the ulnas and radiuses were thickened. Sprengel's deformity was present. The feet were broad and flat. The spine had a prominent dorsal curve, with mild kyphosis.

Fig. 7 (case 3).—Dwarfism, large head, short neck, pot belly, umbilical hernia and other typical changes; age, 9 years.

Fig. 8 (case 3).—Typical facies, with hazy corneas.

Ocular Examination: The eyes seemed slightly protuberant and the lids heavy. Examination with a chart for illiterates showed that unimproved vision was 10/200 in the right eye and 10/200 in the left.

The right cornea seemed large and measured 13 mm. It was diffusely cloudy, especially when oblique illumination was employed. The pupillary actions were normal. During anesthesia the fundus was seen with difficulty but was grossly normal.

The left cornea measured 13 mm. and was hazy, like the right. The pupillary actions were normal and the fundus grossly normal.

The intraocular tension was 22 in the right eye and 19 in the left eye (Schiøtz).

Slit lamp examination revealed that the epithelium and endothelium were normal. Scattered throughout the stroma were small punctate dots like those

Fig. 9 (case 3).—Slit lamp picture, showing small punctate dots (lipid granules) scattered through the middle and posterior layers.

seen in case 2. These dots became somewhat larger and more numerous in the deeper layers (fig. 9).

Laboratory Examination: Examination of the blood showed, per hundred cubic centimeters: fatty acids, 642 mg.; total cholesterol, 308 mg.; phospholipid, 272 mg., and total lipids, 1,060 mg. Puncture of the sternal marrow disclosed large granules present in the leukocytes, azurophilic and basophilic in type, and predominating in the polymorphonuclear cells of all stages. The blood count was normal except that there were granules in the polymorphonuclear leukocytes. The reaction to tuberculin was negative. The urine was normal.

Psychometric Test: Examination with Stanford-Binet form L disclosed a mental age of 5 years and 10 months. The intelligence quotient was 65. The child was classified as a moron.

Roentgenologic Examination: Roentgenograms showed the skull to be scaphocephalic, the sella elongated and flat and the maxilla underdeveloped. The mandible

was abnormal in that the ascending ramus was almost absent. The remainder of the bony changes were like those in case 1. The bone age of the patient was given as 6½ years (fig. 10).

Course.—The patient continues under the observation of Dr. Reilly.

Fig. 10 (case 3).—The bony changes.

CASE 4.—J. P. P. (fig. 11), a boy born July 8, 1935, was admitted to the University of California Hospital Oct. 3, 1940 for study and observation.

History.—The family history disclosed nothing important except that a younger brother (patient 5) also had had the disease. The parents were unrelated. There had been twins on the mother's and the father's side in the past first and second generations.

The patient was apparently normal at birth. Teeth appeared when he was between 6 and 7 months old; he walked at 19 to 20 months. The hearing was normal until he was 2 years of age; since that time he has gradually become deaf. He talked in monosyllables at 14 to 15 months but does not talk now, although he can make his wants known.

The first signs of dysostosis multiplex appeared at the age of 5 months, when the mother noted "golf-ball-sized," symmetric, firm, nontender "bumps" over the lumbar region at the midline. At 1½ years the facies began to change. The head assumed a peculiar shape; the lower jaw became enlarged and the tongue thick. The abdomen became protuberant, and an umbilical hernia developed. The hands became enlarged and the ankles thick. There was also an abnormal

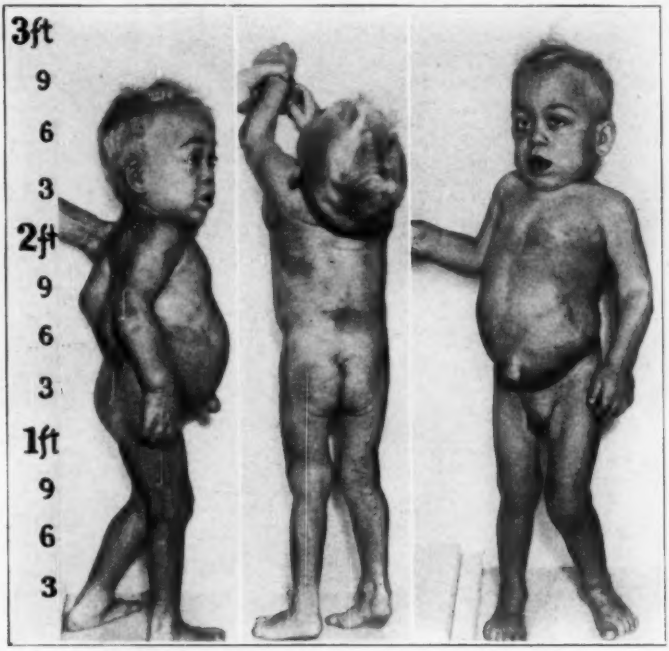

Fig. 11 (case 4).—Dwarfism, typical facies, pot belly and umbilical hernia; age, 5 years.

distribution of fat. There has been no growth during the last two years, and the weight and height have remained unaltered. The skin has become thickened and "puffy."

Examination.—The height was 34 inches (86 cm.). The appearance was typical of Hurler's syndrome. The head was large and scaphocephalic, with prominent frontal bosses. The orbits were widely separated and the eyes large. There was a typical saddle nose with flaring nares. The lower jaw was broad, the lips somewhat thickened and the tongue large. The teeth were peg shaped and widely separated. The skin was coarse and dry, and there were erythematous areas over the back, buttocks, abdomen and neck. The patient was almost deaf. The neck was thick and short; the chest was round, with a protuberant sternum, and the scapulas were large and winged. The abdomen was very protuberant, with a

pendulous umbilical hernia that was reducible. The liver and spleen were enlarged. The patient walked with a limp because the right leg was shorter than the left. The extremities were small as compared with the head and trunk, with marked thickening at the distal ends of the radiuses, ulnas, tibias and fibulas. The hands were thick and large, with thickened fingers that could not be entirely extended. There was kyphosis in the lumbar region.

There was hypertension, more marked in the legs than in the arms. The measurements were as follows: right arm, 132 systolic and 0 diastolic; right leg, 180 and 112; left arm, 134 and 101; left leg, 142 and 108.

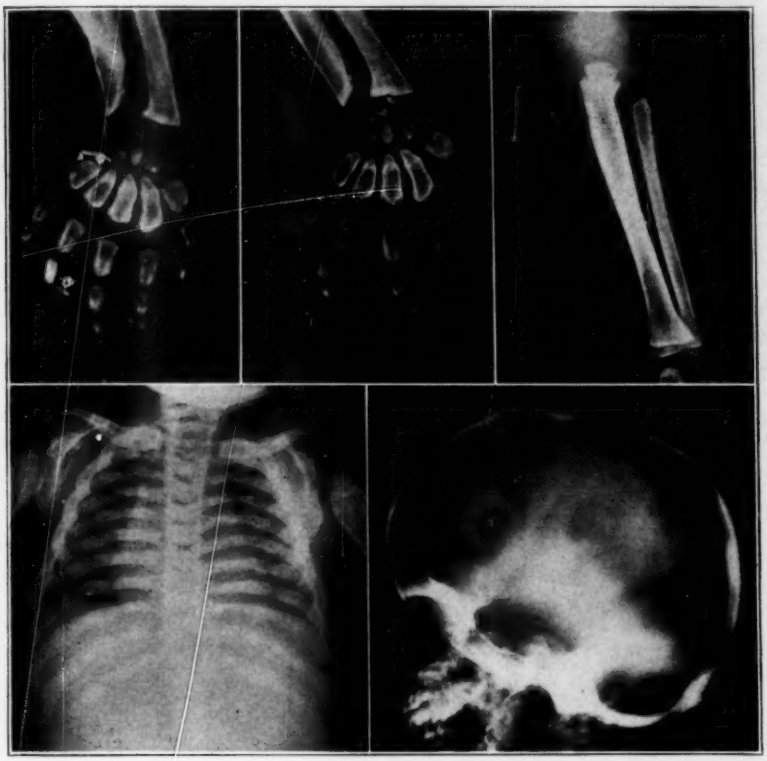

Fig. 12 (case 4).—The bony changes.

Ocular Examination: There was internal strabismus of the left eye of 10 degrees. This was said to be less than in the preceding year.

Visual acuity could not be obtained, but the child had no apparent difficulty with vision. The eyes were mildly exophthalmic.

The right cornea was slightly enlarged; it measured 13 mm. There was a uniform haziness of the cornea, especially with oblique illumination. The iris was normal. The pupil was equal to the left, was regular and reacted to light. The fundus was normal.

The left cornea measured 13 mm. in diameter and showed the same cloudiness noted in the right. The pupil and the fundus were normal.

The intraocular tension could not be obtained with the tonometer but seemed normal on palpation.

Slit lamp examination showed fine gray to grayish yellow punctate spots scattered throughout the stroma like those noted in the other cases.

Laboratory Examination: The Wassermann and the Kolmer test were negative, as was the reaction to tuberculin. Urinalysis gave negative results. The blood showed 80 per cent hemoglobin, with a white cell count of 4,600 and a differential count of 57 per cent neutrophils and 37 per cent lymphocytes.

Roentgenologic Examination: The report is from the division of roentgenology.

The skull was large, with the frontal bone bulging forward and the occiput bulging downward. There was such deformity in the region of the sella that apparently only the dorsum sellae remained. The ribs were noticeably widened and the vertebral articulations deformed; the ends showed irregularity and incomplete development. The upper ends of the humeri were irregular and the epiphyses fairly well formed. The dorsal spine showed some convexity of the upper and lower surfaces of the vertebral bodies. The lumbar spine showed pronounced deformity and incomplete growth of the first lumbar vertebra. The upper acetabular margins were slanted upward, and there was irregularity in the bony cortex.

The phalanges of the hands were widened and pointed at the distal ends. The metacarpal bones were widened and pointed more or less at their proximal ends. The distal ends of the ulnas were deformed, with the distal faces looking radialward about 45 degrees (fig. 12).

Course.—The patient continues under the observation of Dr. Reilly.

CASE 5.—D. P. (fig. 13), a white boy born Feb. 13, 1937, was seen at the University of California Hospital on Oct. 3, 1940, having been sent in for observation.

History.—The patient was a dissimilar twin whose sister developed normally. In addition to his twin sister he had an older brother (patient 4), who had the disease.

He was born after his twin. When the father first saw the infants he remarked that the patient would be "the slow one" of the two. An umbilical hernia was noticed at birth. Aside from this nothing unusual was observed until the patient was 5 months old. At this time, when the child started to sit up, spinal kyphosis was observed as a hard bony "lump on the lower part of the spine." By the time the child was a year old the parents had noted the large head, the big hands with fingers always partially flexed and the general similarity to the older boy. The child, in contradistinction to his brother, is still growing in height and weight. His normal twin sister, however, is "a head taller" and has a large vocabulary. The patient can hear and understand simple commands such as a request to fetch his mother's shoes. He does not talk but indicates his wants by going to the faucet, the food cupboard, etc. He is a friendly child.

Examination.—The height was 35 inches (89 cm.) and the weight 14.52 Kg. The circumference of the head (occipital frontal) was 56.5 cm., the biparietal diameter 19.5 cm. and the frontal-occipital diameter 24 cm.

The patient presented the classic picture of dysostosis multiplex. The head was large, with prominent frontal bosses. The orbits were widely spread. The

lower jaw was broad and the mouth big, with pointed, widely separated teeth. The tongue was larger and thicker than normal but not as enlarged as that of the patient's brother. The typical saddle nose with flaring nares was also present. The neck appeared to be nonexistent. The abdomen was very protuberant and had a large reducible hernia. The extremities were relatively small, with thick, big hands and feet. There was a large plateau-shaped kyphos in the lumbar region. The hearing was apparently not impaired.

Ocular Examination: The eyes were mildly exophthalmic, and the lids were heavy. It was not possible to obtain the visual acuity, but there appeared to be no gross reduction.

The right cornea measured 13.5 mm., was uniformly hazy and with oblique illumination appeared to be opaque. The pupil reacted normally. Fundus examination gave negative results.

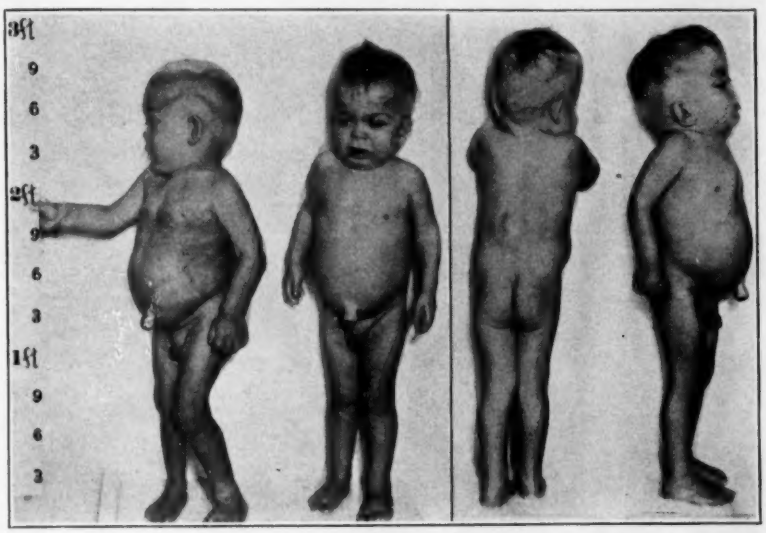

Fig. 13.—Patient 5, aged 3 years and 6 months, at right; his brother, patient 4, at left.

The left cornea was slightly enlarged (13.5 mm.) and uniformly hazy. The pupil showed no abnormality, and fundus examination gave negative results.

Slit lamp examination showed the typical grayish punctate dots scattered throughout the corneal stroma but more marked in the deeper layers.

The intraocular tension could not be obtained with the tonometer but appeared normal on palpation.

The blood pressure was slightly elevated in the legs. In the right arm it was 124 systolic and 0 diastolic; in the right leg, 128 and 70; in the left arm, 118 and 60; in the left leg, 132 and 72.

Laboratory Examination: The Wassermann and the Kolmer test were negative, as was the reaction to tuberculin. Urinalysis gave negative results. Examination of the blood showed hemoglobin 82 per cent and white cells 4,200, 60 per cent being neutrophils, 2 per cent eosinophils, 1 per cent basophils, 33 per cent

small lymphocytes, 4 per cent large monocytes and 10 per cent nonfilamented neutrophils. An oral dextrose tolerance test showed 4 mg. per hundred cubic centimeters of blood at the end of one-half hour and none at the end of an hour.

Roentgenologic Examination: The findings were almost identical with those in case 4 and need not be repeated here. The bone age was given as 3 years (fig. 14).

Course.—The patient continues under the observation of Dr. Reilly.

Fig. 14 (case 5).—Roentgen findings; bone age, 3 years.

COMMENT

Certain features of the disease are due to a disturbance of lipid metabolism. For this reason dysostosis multiplex has been classed among the lipoidoses, which include a variety of conditions in which there is abnormal storage of lipid-like substances in the tissues. The stored lipid is accumulated in reticuloendothelial cells, notably in the brain, corneas, pituitary gland, liver, spleen and lymph nodes. It is deposited in the cells in the form of fine granules in the cytoplasm,

and its exact chemical nature is not known. The differentiating factor in the diagnosis of the lipoidoses depends not only on the organs in which the lipid is stored but also on the nature of the lipid itself. Constitutional disturbances of lipid metabolism have been discussed in detail by Rowland.[29] They are limited primarily to five diseases.

Tay-Sachs disease, or amaurotic family idiocy, which occurs in several forms, is characterized by a cherry red spot in the macular region with subsequent optic nerve atrophy. There are progressive paralysis, convulsions and idioc . In both the infantile and the juvenile form there is widespread degeneration of the ganglion cells of the retina and of the central nervous system. In the juvenile form the degeneration seems to be accompanied by lipid infiltration. The deposit of lipid is found in the form of a phosphatide with its site of predilection in the nervous system, muscle and glial cells. According to Tuthill,[16] at autopsy the changes observed in the brain are identical with those seen in dysostosis multiplex.

Niemann-Pick disease, which resembles Tay-Sachs disease, also occurs in infants. It is familial, is found mainly in the Jewish race and terminates life at the end of the second year. The characteristic fundus picture of amaurotic family idiocy may or may not be present. This syndrome includes enlargement of the liver and spleen together with brownness of the skin. According to Kressler and Aegerter,[4] the presence of large foam cells is the predominating histopathologic change, and the infiltrating material is mostly a phospholipid which takes fat stains after mordanting and shows anisotropic bodies with polarized light. Rowland [29] stated that large amounts of lipids, particularly phosphatides, are stored in reticuloendothelial and other cells.

Hand-Schüller-Christian disease is characterized by progressive decalcifications of the cranial and other flat bones, exophthalmos and the presence of diabetes insipidus. In this disease the whole body may be involved, the chemical deposit being in the form of cholesterol or its esters found in the large foam cells.

Gaucher's disease is familial and characterized by splenomegaly, hepatomegaly, anemia and hemorrhages and in the later stages by wedge-shaped conjunctival thickenings at the limbus in the palpebral fissure. The bone marrow and lymph glands may also be involved. The disease may run a chronic course. An infantile form similar to Tay-Sachs disease has been reported. The lipid stored in Gaucher's disease is kerasin, which is not normally found in the body.

Dysostosis multiplex (Hurler's syndrome) shows an infiltration of a lipid-like substance primarily in the liver, spleen, lymph nodes and anterior lobe of the pituitary gland. From Berliner's [19] work it is

29. Rowland, R. S., in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1937, vol. 3, chap. 23, p. 15.

known that this also involves the corneas. The deposits of lipid appear in the form of fine, curved, rodlike granules whose exact chemical nature is as yet undetermined but which are probably a complex compound of lipid and protein.

In addition to the lipid change in dysostosis multiplex, the bony alterations are typical. There is no explanation for the fact that the bony changes are coexistent with the lipid disturbance. As Washington [11] has pointed out, the bony changes are not secondary to the lipid disease, as lipid deposits cannot be found in or about the cartilage cells. Also, in other lipid diseases there are no bony changes similar to those of Hurler's disease. Thus the outstanding features of dysostosis multiplex can be divided into those resulting from bony changes and those that are secondary to the infiltration of lipid into various organs.

The enlargement of the skull, according to Washington,[11] is due to a defect in the mesodermal anlage of the top of the skull. The depression of the nose, widening of the orbits and elongation of the sella turcica seen in roentgenograms seem to result from abnormal development of the sphenoid bone. Kyphosis results from stress on the bodies of vertebrae whose cartilages have failed to develop. The dwarfing is caused by a disturbance in epiphysial growth, while restriction of motion in the finger, wrist and elbow joints is due to poor formation of the articular surfaces.

The lipid infiltration of the central nervous system causes the mental and the sexual retardation. The usual enlargement of the liver and spleen is the result of infiltration by the offending lipid-like substance. The clouding of the corneas which is so characteristic of the disease is also the result of this infiltration.

The prognosis is unfavorable; in most instances death occurs before the age of 20. The patients reported on by Ruggles [8] in 1931 were seen by us in 1940 and were then aged 24, 20 and 13. They showed certain features, however, that make one wonder whether or not they had true dysostosis multiplex. The pediatrician was unwilling to make a definite diagnosis. In dysostosis multiplex death usually results from heart failure or infection of the respiratory tract, to which the patient is particularly liable.

Differential Diagnosis.—The striking resemblance of the patients to one another, together with the characteristic signs they present, makes the diagnosis relatively easy.

Morquio in 1929 [30] and again in 1935 [31] described a bony disease that simulates dysostosis multiplex. It is a generalized bony abnormality starting between the ages of 1 and 4 years and results in dwarfing,

30. Morquio, L.: Arch. de méd. d. enf. **32**:129, 1929.
31. Morquio, L.: Arch. de méd. d. enf. **38**:5, 1935.

marked deformities of the thorax, kyphosis of the spine, grotesque flexion deformities of the knee and hip joints and general retardation. Usually the intelligence is unimpaired. The disease is due to defects in the orderly growth of ossifying cartilage. Shelling [32] considered it to be a forme fruste of achondroplasia. There is a familial factor, and according to Jacobsen [33] the disease is sex linked and follows a definite hereditary pattern. In the family he reported there was a history of 20 cases in five generations.

Although various ocular defects have been present, Meyer and Brennemann [34] stated that no characteristic ocular involvement has been reported. Barnett [35] and Freeman [36] emphasized the fact that the eyes were abnormally widely spread. Veasey,[12] who has reviewed the subject of the ocular findings in Morquio's disease, discovered in the literature several instances of blurred disk. There were also reports of signs of cervical sympathetic irritations which were attributed to lesions in the spine and the compression of the neurovascular pedicle of the eyeball.

The principal differentiation lies in the fact that Morquio's disease is not manifest until the age of walking, there is a definite familial tendency, there is no limitation of motion in the extremities, the head shows no changes, the mentality is good and there are no characteristic ocular changes. Washington,[11] however, expressed the opinion that the two diseases may be related.

Rickets is more easily differentiated because of the absence of severe bony malformations and corneal cloudiness. The roentgenologic findings in rickets are not limited to the epiphyses. In dysostosis multiplex the ends of the bones are irregular and fragmented, as contrasted with the cupping, fraying and fuzzy appearance of the epiphyses in rickets. Although dwarfing may occur in rickets, it is not severe, and the body height can be improved by proper diet.

There is no evidence to indicate that dysostosis multiplex is one of the endocrine disturbances. Kressler and Aegerter [4] stated that cretinism has been mistaken for this disease but that Hurler's disease fails to respond to thyroid treatment. In addition, the histologic studies of the thyroid gland in their case did not reveal the changes usually described in severe hypothyroidism.

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32. Shelling, D. H., in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1937, vol. 4, chap. 29, p. 1.

33. Jacobsen, A. W.: Hereditary Osteochondrodystrophia Deformans: Family with Twenty Members Affected in Five Generations, J. A. M. A. **113**:121 (July 8) 1939.

34. Meyer, H. F., and Brennemann, J.: Rare Osseous Dystrophy (Morquio), Am. J. Dis. Child. **43**:132 (Jan.) 1932.

35. Barnett, E. J.: J. Pediat. **2**:651 (June) 1933.

36. Freeman, J.: Morquio's Disease, Am. J. Dis. Child. **55**:343 (Feb.) 1938.

Children with hypothyroidism show none of the signs which are due to lipid dysfunction, such as cloudiness of the corneas. Also, they have no gross bony deformities such as those seen in dysostosis multiplex.

Other forms of dwarfing can also be differentiated by the non-appearance of the classic signs of this disease.

The failure to develop, the saddle nose, the bony defects, the poor hearing and the diffusely cloudy corneas might suggest congenital syphilis. In fact, the ocular condition of patient 3 of our series was diagnosed as interstitial keratitis, and the child was treated as syphilitic for six months. In the cases of dysostosis multiplex reported, the Wassermann test has been almost universally reported as negative. In addition, the bony changes of syphilis are periosteal and not greatly deforming. The possibility of interstitial keratitis can be ruled out by slit lamp examination, which in the case of dysostosis multiplex shows the typical picture described.

Degenerative dysostosis is of two forms. According to Husler [5] there is (*a*) the form with pathologic ossification and (*b*) that with defective ossification. Dysostosis cleidocranialis (Scheuthauer, Marie and Sainton) is of the hypoplastic form in contrast to dysostosis multiplex (lipochondrodysplasia). Dystrophia periostalis hyperplastica familiaris (Dzierzynski) may include bony changes which are very similar, but the lipid changes fail to develop. It may be related to dysostosis multiplex. Dysostosis craniofacialis (Crouzon) exhibits hyperostoses on the forehead and parietal bones affecting the outer plate. Prognathism, delayed closure of the fontanels, hooked nose, divergent squint and clavicular defects serve to distinguish it.

The possibility that the corneal changes are degenerative has been discussed in detail by Gasteiger and Liebenam.[10] As they pointed out, it is evident from the appearance and course that the various types of ribbon-shaped or band-shaped areas of degenerative keratitis, which appear at various ages and are usually monocular, can be ruled out. The intact epithelium and endothelium would exclude the possibility of epithelial or endothelial dystrophy.

They said that among the corneal degenerations those described by Axenfeld must be ruled out, namely fatty degeneration, dystrophia calcarea, dystrophia urica and dystrophia myxedematodes. These changes occur at various ages and belong in the classification indicated by the name. In the fatty degeneration there are yellow opacities which according to Elschnig [37] are usually central and only rarely peripheral. Under the slit lamp they appear as clumps, lines or points that lie closely associated in some areas of the cornea while the remainder is free from changes. New formation of vessels also occurs.

37. Elschnig, H. H.: Klin. Monatsbl. f. Augenh. **71**:720, 1923.

Gasteiger and Liebenam [10] further pointed out that dystrophia calcarea, originally described by Axenfeld,[38] shows dense white nodules or linear opacities extending from the periphery into the cornea and producing a rather uniform clouding. Dystrophia urica, a rare condition described by Uhthoff,[39] shows a deep yellow-gray clouding composed of small goldlike punctate opacities which extend from the limbus toward the center of the cornea. The myxedematous dystrophy described by Axenfeld consists of white areas which at first appear in the periphery of the cornea and gradually spread. Later the central part of the cornea becomes involved, and vascularization appears. From our review of the subject we feel it is apparent that the corneal changes in dysostosis multiplex do not belong to the group of degenerative changes described.

There remain those corneal lesions that occur without vascularization and are characterized by a familial tendency. According to Bücklers [40] they can be divided into three types. The first is the crumbling type limited to the center of the cornea. The second is the punctate, or speckled, type, which in the far advanced stages may extend over the entire cornea and in places may involve the epithelium. The third type is the lattice-like degeneration described by Haab-Dimmer. In it, corneal sensitivity is usually reduced, which is not the case in dysostosis multiplex.

As Meyer and Okner [17] have pointed out, other isolated, unclassified cases of corneal degeneration have been reported. For the most part the patients have shown small punctate opacities in the corneal parenchyma.

The presence of the typical physical findings together with the slit lamp picture makes the diagnosis of the corneal involvement in dysostosis multiplex relatively easy.

SUMMARY

Dysostosis multiplex is a rare congenital disease recognized as a clinical entity by Hurler in 1919. The disease usually appears at the age of 1 year and is characterized by bony defects and disturbances in the storage of lipid, the nature of which is still unknown. A careful search of the literature revealed that, including those described here, 50 cases have been reported.

The malady is a form of dwarfism in which there are scaphocephalic deformities of the skull and chondrodystrophic changes in other parts of the body. The head is large; the nose is a saddle nose with flaring nares. The alveolar processes are large and the tongue thick and fleshy.

38. Axenfeld, T.: Klin. Monatsbl. f. Augenh. **48**:58, 1917.

39. Uhthoff, W.: Klin. Monatsbl. f. Augenh. **54**:383, 1915.

40. Bücklers, M.: Ber. ü. d. Versamml. d. deutsch. ophth. Gesellsch. **51**:103, 1936.

The neck is short, the spine kyphotic and the belly protuberant, with an umbilical hernia. The liver and spleen are enlarged. The limbs are short, with limitation of motion in the joints.

Wide separation of the orbits, prominence of the globes and bilateral corneal clouding are characteristic ocular defects and occur in 75 per cent of the cases. Slit lamp examination of the corneas reveals a diffuse infiltration of small punctate dots, varying in size and yellowish gray in color, which are scattered through the corneal stroma. These infiltrates have been identified as lipid deposits.

Dysostosis multiplex belongs to a group of diseases characterized by disturbances in the storage of lipid. Other members of this group are Niemann-Pick disease, Hand-Schüller-Christian disease, Gaucher's disease and Tay-Sachs disease.

Five cases of dysostosis multiplex, occurring in three families, are reported. Two of the patients from different families were twins. Patient 1 was a girl whose twin sister was unaffected, while patient 4 was a boy whose twin sister did not have the disease.

In all 5 of the patients both corneas were involved. Slit lamp examination was employed in 4 cases, and the findings were identical with those which have been described as typical of the disease.

EXPERIENCES WITH IRIDENCLEISIS

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The underlying theory of most modern operations for glaucoma is the creation of an artificial drainage channel from the anterior chamber to the loose subconjunctival tissues. The earlier operations, such as trephining and anterior sclerectomy, provide no means for keeping open the artificial channel through the sclera. Spontaneous closure of this channel by the natural healing processes is one of the two chief causes for failure in these operations. The other chief cause of failure is the improper preparation of the flap beneath which diffusion and absorption of the excessive aqueous is to occur. In the more recent operations, such as iridencleisis, iridotasis and other iris inclusion operations, an attempt is made to prevent healing and closure of the drainage canal by the interposition of iridic tissue, which also will act as a wick or seton. A serious objection to some of the operations of this type is the resultant traction on the iris and the ciliary body.

Holth is regarded generally as the originator of iridencleisis. The following brief description of his operation, for which he designed special instruments, is taken from his 1930 paper:[1]

> The point [of the keratome] splits the bulbar conjunctiva, 8 mm. from the corneal border. By very short transverse zigzag movements of the keratome's point the conjunctival fold is slid over the sclera toward the limbus. If the anterior chamber is of normal depth, the scleral incision is made from 1.5 to 2 mm. from the corneal limbus and the keratome's blade is guided parallel with the iris plane . . . ; then the length of both the conjunctival and the limbal incisions is exactly 6 mm., which is the width of the subconjunctival tunnel connecting the two incisions. . . . he [the surgeon] grasps the iris near the edge of the pupil and draws the iris out so far that the upper part of the pupil and, through this, the pigment epithelium on the back of the iridial tent are seen just outside the limbal incision. . . . Through the extralimbal part of the pupil the surgeon inserts the one blunt blade of de Wecker's iris scissors underneath the back of the iridial tent, while the other blade rests on the front of the tent. . . . He now releases the iris from the forceps (the iridial tent lies between the two blades of the scissors) and removes the iris forceps altogether from the field of operation. . . . The meridional clip through the iridial tent is now made; the two sphincter angles of the narrow coloboma caused by the iridotomia retract somewhat into the anterior chamber. . . .

1. Holth, S.: Iridencleisis cum Iridotomia Meridionali: Operative Method Both in Acute and in Chronic Primary Glaucoma, Arch. Ophth. **4**:803 (Dec.) 1930.

Holth's article is not clear about the level at which the subconjunctival tunnel should be made. In my opinion, as I shall discuss later, the level of the dissection down to the limbus is of vital importance.

In 1930 Greenwood [2] described a somewhat different form of iris inclusion operation, which eliminated the objection to Holth's operation —the pull on the iris. He made two radial cuts through the iris from sphincter toward base and isolated a tongue of iris which he turned back, pigmented side uppermost, through the scleral incision and beneath the flap. He also performed a sclerectomy to increase the opening through the sclera. Like Holth, Greenwood mentioned little about the flap. He stated: "A conjunctival flap is then made fairly high up, the same as would be made for a trephining, and separated from the sclera with as little cutting as possible, being especially careful that the subconjunctiyal tissue is incorporated in the flap."

Greenwood's operation appealed so much to me that I immediately started doing it. The results were so uniformly successful that I adopted it as the operation of choice for primary glaucoma—for both the congestive and the noncongestive type. I have performed it approximately one hundred times and am aware of only two failures when it was properly performed. Unfortunately, changes in my hospital affiliations make it impossible for me to present statistics. The other failures that I have observed occurred in patients operated on by interns and other physicians who either disregarded or misunderstood instructions, particularly for the dissection of the flap.

Before making a sudden large opening into a hard eyeball one should perform a preliminary paracentesis. A narrow cataract knife should be made to enter the anterior chamber subconjunctivally, and some of the aqueous should be allowed to run out by turning the knife to separate the sides of the scleral wound. The paracentesis is best done midway between the lateral and the inferior rectus muscle. Ten minutes later one may proceed with the main operation.

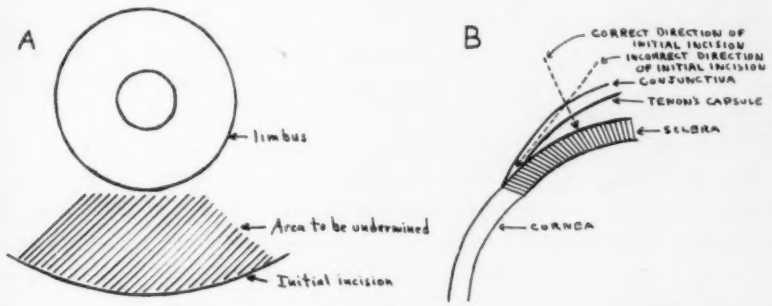
A urologist would consider it wrong to decompress a distended bladder suddenly. Similarly, the ophthalmologist always should avoid sudden full decompression of a hard eyeball with the resultant hemorrhages and violent displacement of intraocular contents.

The most important step in the operation of iridencleisis, and the one on which its success or failure largely hinges, is the dissection of the flap beneath which diffusion of the aqueous is to occur. The initial incision should be made about 7 mm. above the limbus, as shown in the accompanying illustration (*A*), in a slightly curved direction, with the concavity toward the limbus. A firm grasp of both the conjunctiva and

2. Greenwood, A.: Combined Iridencleisis and Sclerectomy for Chronic Glaucoma, Am. J. Ophth. **13**:301 (April) 1930.

the underlying tissues must be made with a toothed forceps. It is important to pinch together between the blades of the forceps as much of the subconjunctival tissues as possible. This will help to bring the incision down to the sclera. Then with Stevens scissors a firm cut is made right down to the sclera. The scissors should be held in a plane perpendicular to the underlying sclera and should not be tilted down toward the sclera so that the points are directed toward the cornea.

There are two potential spaces through which diffusion and absorption of the aqueous may take place—the space between Tenon's capsule and the conjunctiva, which is filled by loose areolar tissue, and the deeper subcapsular, or episcleral, space between Tenon's capsule and the sclera, which also is filled with loose tissue. About 3 mm. from the limbus Tenon's capsule fuses with the sclera, thus obliterating the deeper space. It is necessary for the initial incision to cut through the outer



A, the area of flap that must be dissected. *B*, the correct and the incorrect directions for the initial incision for the flap. An incorrect incisional direction may fail entirely to open up the space between the sclera and Tenon's capsule. Also, it causes excessive formation of scar tissue in the subconjunctival space. The injection of a small amount of procaine hydrochloride beneath both the conjunctiva and Tenon's capsule will make the dissection a little easier.

space perpendicularly and not obliquely. A diagonal or oblique incision not only will increase the amount of subsequent scar tissue, which in turn will hinder the permeation of aqueous (*B* in the accompanying illustration), but may reach the sclera in front of the place where the sclera and Tenon's capsule fuse. The occurrence of the latter possibility would leave the lower space unopened and unavailable for absorption.

After the initial incision has been made directly down to the sclera it should be extended on each side until it reaches a little beyond the projections of the medial and the temporal edges of the cornea (*A*). Then an approximately trapezoidal area of flap should be undermined down to within 0.5 mm. of the limbus in the midline. On each side of the midline the dissection need not approach the limbus so closely. The

avoidance of any extension of the flap into the cornea produces a thicker and therefore safer flap at the corneal end. Only enough area of flap should be undermined to permit the turning over of the flap on to the cornea. In the dissection of the flap it is important that no blunt separation of the tissues and no spreading of the scissor blades be done. Short successive cuts should be made with the points of the scissors directed obliquely down to the sclera. Spreading of the blades of the scissors between cuts would pull the tissue fibers apart and cause far more subsequent cicatricial tissue than sharp severance of the fibers without traction. The more scar tissue in the diffusion space the less the drainage that will be possible.

The anatomic considerations involved in the type of flap which I recommend have also been stressed by Fralick, of Michigan, in his lecture on applied anatomy, and more recently by Benedict.[3]

After the flap has been prepared a single suture may be inserted into the center of its edge. This can be used by the assistant as a traction suture for pulling the flap down over the cornea while the other steps of the operation are performed. At the end of the operation this suture may be used, along with two others—one on each side—for closing the conjunctival incision.

The point of the keratome should enter the sclera about 2 mm. behind the limbus. A medium-sized incision—not more than 5 mm.—should be made into the anterior chamber. On withdrawal of the keratome, which should be slow, the keratome may be rotated progressively so as to fill the scleral wound as much as possible and thereby prevent a too rapid emptying of the anterior chamber and prolapse of the iris.

Next, before the two iridotomy incisions are made, a small sclerectomy should be done on the corneal lip of the scleral incision. A smaller wedge of sclera should be excised than in the Lagrange operation. This step, while desirable, is not vital to the success of the operation and may be omitted if prolapse or impending prolapse of the iris makes it likely to result in a horizontal, buttonhole perforation of the iris.

The iris can be pulled into and through the scleral incision, pigmented surface up, with an iris forceps. Then two radial incisions about 2.5 to 3 mm. apart should be made through the iris from the pupillary border to the base. These can be made best with either straight iris scissors or a de Wecker pince-ciseaux. Thus a tongue of iris will have been isolated. This should be pulled back over the sclera, pigmented surface up. About one fourth of its length should be cut off to prevent its reaching too near the conjunctival opening.

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3. Benedict, W. L.: Sclerocorneal Trephining (Elliot's Operation), Arch. Ophth. **24**:1100 (Dec.) 1940.

Finally, the flap is pulled back over the tongue of iris and sutured back into place. The eye not operated on need be kept covered only until the next day. Motion of the eyes will aid diffusion of the aqueous.

This operation I have found much more successful than trephining or the Lagrange sclerectomy and vastly superior to cyclodialysis. It has been equally successful in the treatment of congestive and of non-congestive glaucoma. I have performed it once and with success for glaucoma secondary to thrombosis of the central retinal artery. The tension usually falls to between 18 and 22 mm. (Schiøtz) and remains there permanently. The inclination toward early nuclear cataract is the same as with any other tension-reducing operation. I have never performed this operation for glaucoma secondary to uveitis and believe it would be harmful because of the necessary manipulation of the iris. For this type of glaucoma a small trephining or sclerectomy should be done after a preliminary paracentesis, and the iris should not be touched in any way if to avoid touching it is possible.

CONCLUSIONS

Greenwood's operation if properly performed is almost always successful in the treatment of glaucoma. Its success is largely dependent on a properly prepared flap beneath which permeation of aqueous must occur.

CHEMOTHERAPY IN THE TREATMENT OF GONORRHEAL OPHTHALMIA

RELATIVE EFFECTIVENESS OF SULFANILAMIDE, SULFAPYRIDINE AND SULFATHIAZOLE

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Numerous reports regarding the excellent results from sulfanilamide in the treatment of gonorrheal ophthalmia have appeared in the literature in the past four years. At the same time there have been reported a number of cases in which the response was not satisfactory. For example, there were some cases in which a prolonged period of therapy was required, some in which there were recurrences and a few in which the disease became complicated by corneal involvement. These cases well illustrate the limitations of sulfanilamide therapy and make evident the need for a more effective drug.

Of the many derivatives of sulfanilamide that have been investigated for their chemotherapeutic usefulness, sulfapyridine, sulfathiazole and the more recently introduced compound sulfadiazine (2-[paraaminobenzenesulfonamido]-pyrimidine) have proved to be the most valuable. Sulfanilamide, sulfapyridine and sulfathiazole have been given a clinical trial in the treatment of gonorrheal ophthalmia in the Cleveland City Hospital. Up to the present time there has been no report in the literature regarding the effectiveness of sulfathiazole against gonorrheal ophthalmia, and the only reports concerning sulfapyridine are those from abroad. This communication deals with a study of the relative effectiveness of sulfanilamide, sulfapyridine and sulfathiazole in the treatment of gonorrheal ophthalmia. Also, a brief review of the literature and a recapitulation of the chemical composition and toxicity of the three compounds are given.

HISTORICAL REVIEW

Sulfanilamide was first prepared by Gelmo [1] in 1908 during the course of his investigations on the azo dyes. The following year sulfonamide-containing azo dyes were found to be superior in color

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1. Gelmo, P., cited by Kolmer, J. A.: Progress in Chemotherapy of Bacterial and Other Diseases, Arch. Int. Med. **65**:671 (April) 1940.

fastness to dyestuffs without sulfanilamide groups. The fact that the azo dyes formed firm combinations with the proteins of wool and silk suggested to Eisenberg [2] the possibility that these chemicals might react with bacterial protoplasm, and in 1913 he discovered the in vitro bactericidal action of chrysoidine and suggested its use in therapy. Azo dyes such as pyridium and scarlet red were then introduced into medicine, but it was not until 1932 that the original prontosil (the hydrochloride of 4-sulfamido-2,′4′-diaminoazobenzene) and several other azo dyes were investigated. In this year Domagk, director of the pathologic laboratory in Elberfield, Germany, observed that mice could be protected by this compound from experimentally induced streptococcic septicemia. In 1935 he published his observations on its experimental use in the treatment of streptococcic infections.[3] Tréfouël and his co-workers [4] suggested that the action of both the original prontosil and the so-called soluble prontosil (disodium 4-sulfamidophenyl-2′-azo-7′-acetylamino-1′-hydroxynaphthalene-3′,6′-disulfonate; now known as azosulfamide) was due to a breakdown product. This substance was sulfanilamide. Investigators in both France and England soon began to experiment with sulfanilamide and its derivatives, but no great attention was given in the medical literature to these new discoveries until 1936, when the English investigators published their results. In that year, Colebrook and Kenny [5] communicated observations on the use of the prontosils in the treatment of puerperal sepsis, and Buttle and associates [6] extended the curative value of sulfanilamide to experimental meningococcic infections. The interest of the medical profession throughout the world was quickly aroused, and publications in great profusion soon appeared.

The compound sulfanilamide has thus far formed the basis for a related group of therapeutically active substances. Efforts to produce a drug with greater therapeutic effect and less toxicity have led to the

2. Eisenberg, cited by Goodman, L., in Blumer, G.: The Practitioners Library of Medicine and Surgery, New York, D. Appleton-Century Co., Inc., 1940, supp., chap. 38, p. 371.

3. Domagk, G.: Ein Beitrag zur Chemotherapie der bakteriellen Infektionen, Deutsche med. Wchnschr. **61**:250 (Feb. 15) 1935.

4. Tréfouël, J.; Tréfouël, J. (Mme.); Nitti, F., and Bovet, D.: Activité due p-aminophénylsulfamide sur les infections streptococciques expérimentales de la souris et du lapin, Compt. rend. Soc. de biol. **120**:756, 1935.

5. Colebrook, L., and Kenny, M.: Treatment of Human Puerperal Infections, and of Experimental Infections in Mice, with Prontosil, Lancet **1**:1279 (June 6) 1936; Treatment with Prontosil of Puerperal Infections Due to Hemolytic Streptococci, ibid. **2**:1319 (Dec. 5) 1936.

6. Buttle, G. A. H.; Gray, W. H., and Stephenson, D.: Protection of Mice Against Streptococcal and Other Infections by Para-Aminobenzensulfonamide and Related Substances, Lancet **1**:1286 (June 6) 1936.

production of many compounds, only a few of which have been adaptable for clinical purposes.

One of these is sulfapyridine, a pyridine derivative of sulfanilamide which has the chemical name 2-(paraaminobenzenesulfonamido)-pyridine or 2-sulfanilamidopyridine. It was synthesized by Ewins and Phillips [7] in England, and introduced into clinical use by Whitby [8] in that country. The Council on Pharmacy and Chemistry of the American Medical Association gave it the name of "sulfapyridine" and accepted it for inclusion in "New and Nonofficial Remedies" in 1939.

Sulfathiazole, 2-(paraaminobenzenesulfonamido)-thiazole, was first synthesized in 1939, independently by Fosbinder and Walter,[9] and Lott and Bergeim [10] in the United States. It is a combination of sulfanilamide and derivatives of heterocyclic amines and is a thiazole derivative of sulfapyridine.

Lawrence [11] has shown experimentally that sulfathiazole has a greater bacteriostatic action against the gonococcus than either sulfanilamide or sulfapyridine. Sulfathiazole in a concentration of 1 to 100,000 was sufficient to inhibit the development of organisms in the culture medium within one-half hour. A number of clinical reports indicating the effectiveness of this compound against genital gonorrhea have appeared. Mitchell, Greig, and Uren [12] were among the first to employ it for this disease and used it in 12 cases of acute or chronic gonorrheal urethritis. In 11 there was freedom from gonorrheal discharge within three days. Culp [13] reported that in 4 of 21 cases no gonococci were found in the urethral smear on the day following institution of sulfathiazole treatment and that in 7 cases none were found after two days. Harkness [14] expressed the opinion that sulfathiazole is more rapid in action against

7. Ewins, A. J., and Phillips, M. A., cited in The Clinical Use of Sulfapyridine in Pneumococcic Pneumonia, Rahway, N. J., Merck and Company, 1940, p. 5.

8. Whitby, L. E. H.: Chemotherapy of Pneumococcal and Other Infections with 2-(*p*-Amino-Benzensulphonamido) Pyridine, Lancet **1**:1210 (May 28) 1938.

9. Fosbinder, R. J., and Walter, L. A.: Sulfanilamide Derivatives of Heterocyclic Amines, J. Am. Chem. Soc. **61**:2032 (Aug.) 1939.

10. Lott, W. A., and Bergeim, F. H.: 2-(*p*-Aminobenzenesulfonamido)-Thiazole: A New Chemotherapeutic Agent, J. Am. Chem. Soc. **61**:3593 (Dec.) 1939.

11. Lawrence, C. A.: Bacteriostatic Actions of Three Thiazole Derivatives of Sulfanilamide on Bacteria in Broth Culture, Proc. Soc. Exper. Biol. & Med. **43**: 92 (Jan.) 1940.

12. Mitchell, D. R.; Greig, C. H., and Uren, J. L.: Treatment of Gonorrhea by Chemotherapy, Canad. M. A. J. **42**:533 (June) 1940.

13. Culp, O. S.: Treatment of Gonorrhea with Sulfathiazole, J. Urol. **44**: 367 (Sept.) 1940.

14. Harkness, A. H.: Sulfathiazole in Gonorrhea, Lancet **2**:250 (Aug. 24) 1940.

the gonococcus than either sulfanilamide or sulfapyridine and that the toxic symptoms encountered are almost negligible.

Following the work of Dees and Colston [15] in 1937 in establishing the value of sulfanilamide in the treatment of genital gonorrhea, reports on the effectiveness of this drug in the treatment of gonorrheal ophthalmia began to appear. Hageman,[16] Levy,[17] Fernandez and Fernandez [18] and Willis [19] were among the first to report successful treatment of patients.

After these initial reports, numerous articles appeared on the subject. One of the most noteworthy was that of Barbour and Towsley,[20] who evaluated the results in 55 cases from the literature and reported 15 cases of their own. They reiterated that sulfanilamide therapy had reduced the average duration of the disease from several weeks to several days and that it had diminished the incidence of corneal complications. They favored the use of large doses of the drug. Bower and Frank [21] reported a series of 21 cases in which sulfanilamide was used. In 18 cases negative smears were obtained within an average of two days. Of the remaining 3 cases, a relapse after a seven day course of treatment was suffered in 2. In 1 of these a cure was effected promptly, while in the other a second course of chemotherapy, lasting seventy-seven days, was required. In the third case forty-seven days of treatment was required for cure. Sulfanilamide was given in doses of 15 grains (1 Gm.) per 20 pounds (9.1 Kg.) of body weight until negative smears and clinical improvement were obtained. Guyton [22] in 1939, in presenting an inclusive report on the use of sulfanilamide in ophthalmology, summarized the reports of 104 cases by fifteen authors. He pointed out that a marked effect on the course of the disease is exerted by small doses of sulfanilamide but that results are more satisfactory when larger doses are given, that is doses sufficient to maintain a concentration of sulfanilamide of 5 to 10 mg. per hundred cubic centi-

15. Dees, J. E., and Colston, J. A. C.: Use of Sulfanilamide in Gonococcic Infections, J. A. M. A. **108**:1855 (May 29) 1937.

16. Hageman, P. O.: Clinical Experience in the Use of Sulfanilamide at the New Haven Hospital, J. Pediat. **11**:195 (Aug.) 1937.

17. Levy, G. J.: Treatment of Infectious Disease with Sulfanilamide, Memphis M. J. **12**:192 (Dec.) 1937.

18. Fernandez, L. J., and Fernandez, R. F.: Sulfanilamide in Gonorrheal Ophthalmia, Am. J. Ophth. **21**:763 (July) 1938.

19. Willis, T.: Sulfanilamide in Ophthalmia Neonatorum, Yale J. Biol. & Med. **10**:275 (Jan.) 1938.

20. Barbour, F. A., and Towsley, H. A.: Experience with Sulfanilamide in Treatment of Gonorrheal Ophthalmia, Arch. Ophth. **22**:581 (Oct.) 1939.

21. Bower, A. G., and Frank, W.: Treatment of Gonorrheal Ophthalmia, Am. J. Ophth. **22**:833 (Aug.) 1939.

22. Guyton, J. S.: The Use of Sulfanilamide Compounds in Ophthalmology, Am. J. Ophth. **22**:833 (Aug.) 1939.

meters of blood. He advocated the continued administration of sulfanilamide for about ten days after the first negative smear in order to prevent recurrences.

Abroad, a few reports have dealt with the use of sulfanilamide, but the majority of investigators have used other compounds. Dollfus and co-workers [23] reported successful results with paradiacetylaminodiphenylsulfone (rodilone, or 1 399 F.) in the treatment of 1 patient with gonococcic conjunctivitis. Slobozianu [24] and Dik [25] administered dimethyldisulfanilamide (N^1, N^1-dimethyl-N^4-sulfanilylsulfanilamide [uliron]), a drug widely used in Germany. Lian [26] advised the use of fever induced by intravenous injections of typhoid vaccine and irrigations with 1:4,000 potassium permanganate in conjunction with the oral administration of dimethyldisulfanilamide. In another study [27] he found that adults who suffered corneal involvement with gonorrheal ophthalmia had a low content of vitamin A and of carotene in the blood, suggesting the need of vitamin A as an adjuvant medication. Dimethyldisulfanilamide, which has the disadvantage of often causing severe peripheral neuritis,[28] is rarely used in the United States. Paradiacetylaminodiphenylsulfone is so toxic and produces such intense cyanosis that it has not been regarded favorably; furthermore, it is not available for use in this country.[29]

Jasseron and Morard [30] emphasized the necessity of giving enough sulfanilamide early. They reported 2 cases in which a protracted period of treatment was required and attributed the poor results to the failure to administer sufficiently large doses in the first few days of therapy. The possibility of the development of sulfanilamide-resistant strains of the organism as a result of the administration of small initial doses was

23. Dollfus, M. A.; Di Matteo, and Proux: Essais de chimothérapie des complications oculaires le la gonococcie par le dérivés organiques du soufre, Bull. Soc. d'opht. de Paris **50**:73 (Feb.) 1938.

24. Slobozianu, H.: Die Behandlung der Ophthalmoblenorrhoe mit Uliron, Dermat. Wchnschr. **107**:1089 (Sept. 10) 1938.

25. Dik, J. H. R.: Use of Prontosil and Uliron in Ophthalmology, Geneesk. tjidschr. v. Nederl.-Indië **78**:1614 (July 5) 1938.

26. Lian, S. B.: Therapy with Dimethyl-Disulfanilamide, Ophthalmologica **97**:341 (Aug.) 1939.

27. Lian, S. B.: Relation of Severe Adult Gonorrheal Conjunctivitis and Vitamin A Content of the Blood, cited by Brown, E. V. L., and others: Year Book of the Eye, Ear, Nose and Throat, Chicago, The Year Book Publishers, Inc., 1940, p. 221.

28. Bannick, E. G.; Brown, A. E., and Foster, F. P.: Therapeutic Effectiveness and Toxicity of Sulfanilamide, J. A. M. A. **111**:770 (Aug. 27) 1938.

29. Robertson, D. F.: Personal communication to the author.

30. Jasseron, F., and Morard, G.: Les sulfamides en ophtalmologie, Arch. d'opht. **3**:875, 1940.

suggested. For newborn infants they advised the following doses of the drug: 1 Gm. per day for four days, 0.75 Gm. for two days, 0.5 Gm. for two days and then 0.25 Gm. for the last two days, making a total of 7 Gm. in ten days. For infants 6 to 12 months of age they advised doubling the dose given to newborn infants. The dose was tripled for adults.

Sulfapyridine appears to be the drug of choice abroad. Michie and Webster [31] in 1938 published the first report regarding the use of this compound in the treatment of gonorrheal ophthalmia. Two patients were treated and in 1 there was almost complete arrest of discharge overnight. They considered the drug superior to sulfanilamide. Slobozianu and Herscovici [32] reported on 6 patients treated with sulfapyridine. Two of these, who were premature infants, were cured in three days. The other 4 were cured in four to six days. They considered this compound superior to paradiacetylaminodiphenylsulfone and dimethyldisulfanilamide. Sysi [33] reported on 11 patients successfully treated. In 4 the organisms disappeared from the secretion within twenty-four hours. He found that sulfapyridine was more effective in the treatment of fresh infection than in the treatment of chronic infection. Redslob and co-workers,[34] Charpy and Bizot [35] and Szinegh [36] also reported favorable results.

There has been no convincing evidence to show that the local use of sulfanilamide and its derivatives is of advantage in the treatment of gonorrheal ophthalmia. Glover [37] instilled azosulfamide in the cul-de-sac in conjunction with oral administration of sulfanilamide. Rein and Tibbetts [38] presented a report on 15 patients treated by irrigation of

31. Michie, A. M., and Webster, M. H.: Gonococcal Ophthalmia Treated with 2-(*p*-Aminobenzenesulphonamido) Pyridine, Lancet **2**:373 (Aug. 13) 1938.

32. Slobozianu, H., and Herscovici, P.: Le traitement de conjonctivites gonococcoques des nouveau-nés par les dérivés organiques du soufre, Ann. d'ocul. **176**: 466 (June) 1939.

33. Sysi, R.: Ueber die Behandlung der Conjunctivitis gonorrhoica mit dem Präparat M. & B. 693, Acta ophth. **17**:466, 1939.

34. Redslob, E.; Marx, P.; Dieffenbach, P., and Milaras, T.: Essai de chimothérapie des affections gonococciques et pneumococciques de l'appareil visuel, Bull. Soc. d'opht. de Paris **51**:326 (April) 1939.

35. Charpy, J., and Bizot, M.: Impressions sur le traitement de la blénorragie par le 693, Bull. Soc. franç. de dermat. et syph. (Réunion dermat., Lyon) **46**:455 (April) 1939.

36. Szinegh, B.: Neuere chemotherapeutische Erfahrungen in der Behandlung der Ophthalmogonorrhoe, Ophthalmologica **99**:29 (Feb.) 1940.

37. Glover, L. P.: Some Uses of Sulfanilamide in Ophthalmology, Am. J. Ophth. **22**:180 (Feb.) 1939.

38. Rein, W. J., and Tibbetts, O. B.: Irrigations with Sulfanilamide as a Treatment for Gonorrheal Conjunctivitis, Am. J. Ophth. **22**:1126 (Oct.) 1939.

the infected eye with 0.5 per cent sulfanilamide solution every fifteen minutes. Of the 15, 5 received 30 to 60 grains (2 to 4 Gm.) of sulfanilamide daily by mouth. Five of the remaining 10 patients required between ten to eighteen days of treatment before the gonococci disappeared from the secretion. This method of treatment was advocated on the basis of the elimination of the danger of toxic reactions that may attend the internal use of the drug. The results obtained, however, were not as satisfactory as those obtained when the drug was given internally.

MODE OF ACTION

An adequate explanation of the mode of action of sulfanilamide and its derivatives has not yet been supplied. According to Lockwood [39] it is reasonable to assume, however, on the basis of a considerable amount of laboratory evidence, that these drugs act on infectious lesions by producing an environment in the body tissues and fluids which is unfavorable for bacterial multiplication. The action is bacteriostatic, not bactericidal. As the capacity of the bacteria to multiply is suppressed their power of invasion is diminished, and their vitality is finally reduced to a point at which the natural defenses of the body can dispose of them.

Herrold,[40] in discussing these principles as applied to gonococcic infections, added that the very bacteriostatic effect responsible for the dramatic clinical improvement may depress the normal antigenic stimulus by reason of an insufficient number of bacteria; also, that during active therapy viable bacteria may remain despite clinical abatement, and that consequently all decisions regarding cure must wait until administration of the drug is discontinued.

Mengel [41] has shown that sulfanilamide is excreted in the tears soon after oral administration. Wien,[42] working with sulfapyridine, found that the concentration of the drug in the lacrimal secretion is similar to that found in the blood. Chinn and Bellows,[43] working with experimental animals, demonstrated that sulfanilamide and its derivatives are present in the cornea thirty minutes after oral administration. In view of these observations it seems likely that these drugs have a twofold mode of action in conjunctival and in corneal infections. First, there

39. Lockwood, J. S.: Sulfanilamide in Surgical Infections, J. A. M. A. **115**: 1190 (Oct. 5) 1940.

40. Herrold, R. D.: Problems in Gonococcal Infections: Present Status and Future Outlook, Am. J. Syph., Gonor. & Ven. Dis. **23**:319 (May) 1939.

41. Mengel, W. G.: Determination of Sulfanilamide in Aqueous and Vitreous After Conjunctival and Oral Administration, Arch. Ophth. **22**:406 (Sept.) 1939.

42. Wien, R.: Chemotherapy and the Eye, Lancet **1**:1404 (June 17) 1939.

43. Chinn, H., and Bellows, J.: Distribution of Sulfonilyl-2-Aminopyridine in the Body, J. Lab. & Clin. Med. **25**:735 (April) 1940; Penetration of Sulfathiazole in the Eye, Arch. Ophth. **25**:294 (Feb.) 1941.

is direct action on the organisms in the conjunctival and in the corneal tissue, slowing their multiplication and permitting the usual protective mechanisms of the body to eliminate them. Second, the constant presence of the agent in the tears may inhibit to some degree the activity of the organisms in the secretions, thus reducing the possibility of reinfection.

TOXIC REACTIONS OF SULFANILAMIDE

The clinical use of sulfanilamide has resulted in a wide variety of toxic manifestations. The mild reactions, which are also the most common, include cyanosis, nausea, vomiting, headaches, malaise, lassitude, dizziness and various low grade pains, usually in the back and legs. According to Garvin [44] cyanosis is present in some degree in 90 per cent of the cases in which the drug is used. It varies from a mild bluing of the lips or nail beds to an intense slaty discoloration of the entire body. It usually appears shortly after the treatment is started, may disappear during the course of the treatment and uniformly disappears within a few days after the use of the drug is stopped. Although not dangerous, these complications are often alarming to both the patient and the physician if they are not aware of the likelihood of their occurrence. Occasionaly severe cyanosis and vomiting may necessitate discontinuation of the use of the drug.

MAJOR COMPLICATIONS OF SULFANILAMIDE THERAPY

Probably the most common serious complication resulting from the use of sulfanilamide is hemolytic anemia of acute or chronic type. Wood [45] reported its occurrence in 4 per cent of a series of 500 patients. The chronic type is more common, milder in degree and slower in development. If administration of the drug is discontinued and the proper supportive steps are taken, recovery usually occurs.

Acute agranulocytosis is rare but is one of the most serious complications. It usually occurs after the second week of treatment. The most common time for its appearance is between the seventeenth and the twenty-fifth day, although it may appear as late as the fortieth day. Usually the first clinical sign observed is fever.

Sulfanilamide may also cause acute or chronic toxic hepatitis and jaundice. Dermatitis, occasionally of a severe type, may accompany the hepatitis. The mechanism of the injury to the liver is not understood, and its occurrence bears no discernible relation to the dose of sulfanilamide or to the prior status of hepatic function.

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44. Garvin, C. F.: Complications Following Administration of Sulfanilamide, J. A. M. A. **113**:288 (July 22) 1939.

45. Wood, W. B.: Anemia During Sulfanilamide Therapy, J. A. M. A. **111**: 1916 (Nov. 19) 1938.

Drug fever is an extremely common toxic manifestation during the course of sulfanilamide therapy. It may occur at any time from the first to the thirtieth day of treatment, but it is most commonly seen between the fifth and the ninth day. It is usually abrupt in onset, is frequently a precursor to more serious complications and is an important warning sign calling for cessation of medication.

TOXIC MANIFESTATIONS OF SULFAPYRIDINE

The toxic reactions caused by sulfapyridine are similar to those of sulfanilamide. While there is a higher incidence of mild toxic reactions, especially nausea and vomiting, the incidence of severe intoxication is minimal. This is due in part to the shorter course of administration necessary to produce the desired therapeutic results. Renal complications occasionally occur, namely hematuria, renal insufficiency and the formation of renal calculi.

TOXIC REACTIONS OF SULFATHIAZOLE

The most complete presentation of the clinical toxicology of sulfathiazole compared with that of sulfanilamide and sulfapyridine is by Long, Haviland, Edwards and Bliss.[46] Sulfathiazole is least prone to produce nausea and vomiting. It is least likely to produce cyanosis, and when this occurs it is minimal in degree. Jaundice was observed in only 1 instance in a study of 169 patients by Finland and his associates.[47] No instances of acute hemolytic anemia, a common toxic reaction of sulfanilamide, have been reported. In a series of 300 patients treated with sulfathiazole, only 1 instance of agranulocytosis was encountered by Long and Haviland.[48] Sulfathiazole has the disadvantage, however, of causing disturbances of the urinary tract similar to those of sulfapyridine. Crystals of acetylsulfathiazole are frequently found in the urine, but unless accompanied by hematuria and anuria their presence is of no significance.

OCULAR MANIFESTATIONS OF TOXICITY OF SULFANILAMIDE AND ITS DERIVATIVES

Ocular manifestations of sulfanilamide and its derivatives, while rare and usually not serious, are nevertheless alarming to the patient.

46. Long, P. H.; Haviland, J. W.; Edwards, L. B., and Bliss, E. A.: Toxic Manifestations of Sulfanilamide and Its Derivatives, J. A. M. A. **115**:364 (Aug. 3) 1940.

47. Finland, M.; Lowell, E., and Straus, E.: Treatment of Pneumococcal Pneumonias with Sulfapyridine, Sulfathiazole and Serum, Ann. Int. Med. **14**: 1184 (Jan.) 1941.

48. Long, P. H., and Haviland, J. W.: Problem of Pneumonia with Reference to Chemo- and Serotherapy, Ann. Int. Med. **14**:1042 (Dec.) 1940.

Bucy [49] in 1937 reported a case of optic neuritis with central scotoma in a 16 year old girl suffering with streptococcic septicemia who had received sulfanilamide for four days. Duggan,[50] in a recent communication dealing with the treatment of acute retrobulbar neuritis, cited another case of this kind and reported 1 case in which the manifestation followed the taking of sulfapyridine. Landsberg,[51] Spellberg,[52] Lagrange and Laudat [53] and Rittenhouse [54] have reported cases of transient myopia following the use of sulfanilamide. Fänge [55] reported a case in which sulfapyridine had been used. Bristow [56] attributed this to edema of the lens which produced a shortening of its focal length. In all cases the error was correctable with a concave lens. Thorne [57] reported a case of temporary loss of vision caused by spasm of the ciliary muscle. Baker [58] contributed a report of a case of hemorrhage in the fundus of an otherwise healthy eye. Rosenthal,[59] in a study of 2 patients without ocular disease, found that the administration of sulfanilamide caused a narrowing of the angioscotomas. After withdrawal of the drug the angioscotomas returned to normal. No explanation of the clinical significance of this manifestation was offered.

Haviland and Long [60] reported 6 patients with conjunctival reactions in a group of 78 patients treated with sulfathiazole. The lesion

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49. Bucy, P. C.: Toxic Optic Neuritis Resulting from Sulfanilamide, J. A. M. A. **109**:1007 (Sept. 25) 1937.

50. Duggan, W. F.: Acute Retrobulbar Neuritis as a Manifestation of Acute Localized Tissue Anoxia, Arch. Ophth. **25**:299 (Feb.) 1941.

51. Landsberg, M.: Visual Disturbances and Sulfanilamide, J. A. M. A. **113**: 2260 (Dec. 16) 1939.

52. Spellberg, M. A.: Toxicity of Sulfanilamide: Severe Transient Myopia Following Use of Sulfanilamide, Illinois M. J. **75**:366 (April) 1939.

53. Lagrange, H., and Laudat: Myopie spasmodique transitoire accident de la médication organique soufreé, Bull. et mém. Soc. méd. d. hôp. de Paris **55**:883 (June 12) 1939.

54. Rittenhouse, E. A.: Myopia After Use of Sulfanilamide, Arch. Ophth. **24**: 1139 (Dec.) 1940.

55. Fänge, G.: Transitory Myopia Developing After Therapy of Pneumonia with Sulfapyridine, Svenska läk.-tidning. **36**:1197 (June 9) 1939.

56. Bristow, J. H.: Temporary Myopia Due to Sulfanilamide, Arch. Ophth. **24**:799 (Oct.) 1940.

57. Thorne, F. H.; Egan, T., and others: Symposium on Use of Sulfanilamide in Eye Conditions, Am. J. Ophth. **22**:430 (April) 1939.

58. Baker, J. P., Jr.: Sulfanilamide Therapy Followed by Hemorrhages in Fundus of Eye, Virginia M. Monthly **67**:562 (Sept.) 1940.

59. Rosenthal, C. M.: Changes in Angioscotomas Associated with the Administration of Sulfanilamide, Arch. Ophth. **22**:73 (July) 1939.

60. Haviland, J. W., and Long, P. H.: Skin, Conjunctival and Scleral Reactions in Course of Therapy with Sulfathiazole, Bull. Johns Hopkins Hosp. **66**:313 (May) 1940.

consisted of "a scleral and conjunctival injection, restricted in the main to the exposed portions of the bulbar conjunctiva and sclera." A smarting and burning sensation of the eyes and epiphora were the chief symptoms. In 4 of the 6 patients the lesion occurred in conjunction with severe dermatitis. In some of the patients exposure to light apparently was an etiologic factor. The reaction disappeared within forty-eight hours after withdrawal of the drug. In 1 case there was a recurrence when the drug was again administered. Reports that have followed seem to indicate that this is a sufficiently common complication of sulfathiazole therapy to require attention. It generally appeared between the fifth and the ninth day of treatment.

The presence of a yellowish tinge of the sclera may be the first sign of jaundice and hepatic damage. A bluish discoloration of the conjunctiva may be the initial indication of cyanosis, and pallor may be the earliest clinical sign of anemia.

GENERAL MANAGEMENT WITH SULFANILAMIDE AND ITS DERIVATIVES

According to Long and his co-workers [46] when possible every available means of laboratory control should be utilized in following patients who are receiving sulfanilamide or one of its derivatives. White cell counts, determinations of the hemoglobin, and examinations of the urine should always be done when the circumstances permit. However, these authors expressed the conviction that, with the exception of acute leukopenia, all the toxic manifestations which occur in the first two weeks of therapy can be recognized by careful clinical observation. They stated that no physician should hesitate to administer these drugs in therapeutically adequate amounts provided he can see his patient at least once a day. At the time the physician visits the patient who is receiving one of the drugs he should inquire as to his symptoms, especially in respect to headache, aching of the body and malaise, because these complaints are often the precursors of many of the severe toxic reactions. The scleras should be examined for jaundice, the mucous membranes for pallor and the skin for rash. The temperature should always be taken to detect the presence of fever. The approximate total output of urine of patients who are receiving sulfapyridine or sulfathiazole should be noted daily. In the case of infants the number of voidings should be recorded. In this way it is possible to detect oliguria, which may herald approaching anuria. Examination of the urine should include both chemical and microscopic examination for hematuria. If this is associated with oliguria, it is generally considered best to stop giving the drug and to administer fluids in large quantities.

METHOD OF STUDY

The cases included in this study are only those in which the diagnosis of gonorrheal ophthalmia was confirmed by the demonstration of gram-negative intracellular diplococci of typical structure and distribution in stained smears of conjunctival secretions or epithelial scrapings. The smears were examined in practically all cases by two observers. In a majority of these cases a diagnosis of gonorrheal ophthalmia had previously been made at another hospital or by a district physician of the city department of health and the patient sent to the Cleveland City Hospital for treatment.

From July 1938 to the time of this report sulfanilamide or a derivative was administered in 40 cases in which there was a positive diagnosis of gonorrheal ophthalmia. From July 1938 to November 1939 sulfanilamide was used in all cases. Two cases of a later date (cases 19 and 20) were added to this group, making a total of 20 cases. From December 1939 to May 1940 sulfapyridine was used. Case 30 was added to this group, making a total of 10. With the exception of the 3 cases included in the other groups, sulfathiazole was used in all cases from July 1940 to the time of this report.

In the sulfanilamide and sulfapyridine groups, daily smears of the conjunctival secretion were examined. In the case in which treatment was with sulfathiazole, smears were made every four to eight hours after chemotherapy was instituted until a negative smear was obtained. After this, examinations of the secretion were made at daily intervals. All initial negative smears in the sulfathiazole group were confirmed by examination of another specimen within one hour, and after the third negative smear epithelial scrapings were examined for the presence of organisms.

All children and infants were seen daily by members of the department of pediatrics, who kept close observation on their general condition. Pulse rate, temperature and respiratory rate were recorded every four hours. White cell counts and hemoglobin determinations were done every two or three days. Urinalysis, with special attention to the presence of blood and crystals, was done in most of the cases of the sulfapyridine and sulfathiazole groups at least every two days. When possible the daily urinary output was recorded. For infants the number of voidings was recorded. The level of drug in the blood was determined, according to the method of Marshall,[61] in a majority of the cases of the sulfathiazole group and in those of the other groups in which there were signs of toxicity or the patient was refractory to treatment.

61. Marshall, E. K., Jr.: Determination of Sulfanilamide in Blood and Urine, J. Biol. Chem. **122**:263 (Dec.) 1937.

DOSE

The dose of sulfanilamide and of sulfapyridine for infants and children was 0.2 Gm. per kilogram of body weight per day. For infants the dose of sulfathiazole was 0.3 Gm. per kilogram of body weight per day. The three premature infants given sulfathiazole (patients 32, 33 and 40) were given 0.35 Gm. per day. There were only 2 adults in the entire series. They were treated with sulfapyridine and were given 4 Gm. of the drug daily. The patients treated with sulfapyridine and sulfathiazole were given an initial dose of one-half the daily dose. It was considered best to give enough of the drug to maintain a level in the blood of 5 to 10 mg. per hundred cubic centimeters. Larger doses of sulfathiazole than of sulfanilamide and sulfapyridine were required to maintain an adequate concentration in the blood.

The drug was given at four hour intervals. In the case of infants it was dissolved and administered with the feedings. Alkalis were not given with the drug. The parenteral method of administration was not used.

Sulfanilamide was given for three or four days and sulfapyridine and sulfathiazole for one or two days after all evidence of inflammation had subsided and three consecutive daily negative smears had been obtained, in order to forestall any possiblity of recurrence.

ADJUVANT TREATMENT

The routine adjuvant treatment in the sulfanilamide and sulfapyridine groups was as follows:

1. Irrigations with warm boric acid solution were given often enough to keep the cul-de-sac free of secretion. These were usually done every three hours for the first two or three days and three or four times daily when the discharge began to subside.

2. Metaphen in a dilution of 1:2,500 (aqueous) was instilled in the cul-de-sac after every irrigation.

3. Foreign protein in the form of sterile milk was administered in 12 cases of the sulfanilamide group but was omitted in the sulfapyridine and sulfathiazole groups.

4. When corneal involvement was noted atropine sulfate solution was given in sufficient dose and strength to keep the pupils dilated.

The only adjuvant treatment in the sulfathiazole group was boric acid irrigations three or four times a day for the first or second day and then only once or twice daily for the remaining two or three days of treatment.

CRITERIA OF CURE

The criteria of cure consisted of (1) arrest of the discharge and subsidence of the inflammation, (2) obtaining three consecutive daily nega-

tive smears of the conjunctival secretion and (3) in the sulfathiazole group obtaining of one negative epithelial smear besides the negative smears of the secretion.

About a week after discharge from the hospital patients were seen in the outpatient dispensary or were visited in their homes by members of the visiting nurses association of the department of public health and examined for evidence of recurrence.

RESULTS OF TREATMENT

The results in the three therapeutic groups are shown in tables 1, 2 and 3. Twenty patients were treated with sulfanilamide (table 1). Fifteen were newborn infants, and the remainder were between 7 months

TABLE 1.—*Results of Treatment with Sulfanilamide*

Patient	Age	Date of Admission	Duration of Infection Prior to Treatment, Days	Smear First Negative, Days	Duration of Purulent Secretion, Days	Time Required for Cure, Days	Eye Involved	
							Right	Left
1	8 days	7/15/38	4	6	6	8	+	+
2	7 mo	7/23/38	2	2	3	4	+	+
3	9 days	8/22/38	2	3	3	5	+	0
4	14 yr	9/ 5/38	2	2	5	5	0	+
5	3 wk	9/23/38	12	3	5	7	+	+
6	Premature	10/ 8/38	3	5	6	7	+	+
7	10 days	11/29/38	7	3	4	5	0	+
8	9 days	1/ 4/39	3	4	5	6	+	+
9	10 yr	1/ 9/39	4	3	5	5	+	+
10	3 yr	1/27/39	4	2	5	5	+	+
11	11 days	2/ 7/39	11	24	28	28	0	+
12	8 days	2/25/39	?	3	4	5	0	+
13	Premature	3/10/39	?	4	3	6	0	+
14	4 days	8/21/39	1	12	10	14	0	+
15	6 days	10/ 6/39	6	5	3	7	+	+
16	17 mo	10/19/39	4	4	4	6	+	+
17	4 days	11/ 8/39	2	2	2	4	+	+
18	10 days	11/24/39	2	2	2	4	+	0
19	10 days	7/ 8/40	7	2	5	5	+	+
20	Premature	9/23/40	4	6	6	8	+	0

and 14 years of age. The average number of days before the first negative smear was obtained and before the discharge subsided was four and nine-tenths and five and seven-tenths, respectively. The average time required to fulfil the criteria of cure was seven and two-tenths days. When one keeps in mind the variations among different observers regarding the criteria of cure, these results are comparable to those of previous reports. One infant (patient 11) required twenty-eight days of treatment before a cure was effected. Sulfanilamide was given in a dose of 0.75 Gm. per day for sixteen days and then 1 Gm. per day for the remaining twelve days; this was sufficient to raise the level of drug in the blood to 24.8 mg. on one occasion. In patient 14 severe cyanosis necessitated the withdrawal of the drug for one day.

The infection lasted fourteen days in this patient, although the average level of free sulfanilamide in the blood was 12.4 mg. The remaining eighteen patients required four to eight days for cure. There were no corneal complications or relapses. Mild cyanosis was observed in most of the cases. It usually appeared about the fifth or sixth day of treatment. No other toxic manifestations were observed.

The data for the sulfapyridine group are tabulated in table 2. There were 7 infants, 2 children and 1 adult in this group. The average time required for the organisms to disappear from the secretion was two and four-tenths days, for the secretion to subside was three and seven-tenths days and for cure to be established was four and eight-tenths days. The minimum time required for cure was three days, while the maximum was six. In patient 21, who had an area of infiltration of the cornea at the time of admission, the only visible sign of corneal involvement

TABLE 2.—*Results of Treatment with Sulfapyridine*

Patient	Age	Date of Admission	Duration of Infection Prior to Treatment, Days	Smear First Negative, Days	Duration of Purulent Secretion, Days	Time Required for Cure, Days	Eye Involved	
							Right	Left
21	35 yr.	12/15/39	5	3	4	5	+	+
22	16 yr.	1/ 2/40	3	2	5	5	0	+
23	9 days	1/21/40	5	4	3	6	+	+
24	Premature	2/26/40	5	4	5	6	0	+
25	3 days	3/10/40	1	1	3	3	0	+
26	3 days	4/25/40	2	2	4	4	+	+
27	5 days	5/ 4/40	4	3	3	5	+	+
28	2 yr.	5/ 8/40	4	2	2	4	0	+
29	4 days	5/16/40	1	1	6	6	+	+
30	5 yr.	11/10/40	3	2	2	4	0	+

after the cure was a small nebula. A drug rash occurred in patient 30 on the ninth day of sulfapyridine therapy. In this case, the ocular infection was considered cured after four days, but administration of the drug was continued to treat associated vaginitis. Nausea and vomiting were not encountered and cyanosis was minimal in this group.

The results in the sulfathiazole group are summarized in table 3. All 10 patients were infants, the oldest being 6 weeks of age. Definite improvement in all cases was noted overnight. Edema of the lids, chemosis and discharge of a purulent secretion subsided within two days. In 6 cases the organisms disappeared from the secretion within eighteen hours. The maximum time required for cure was four days. The averages were as follows: smears first negative, twenty-four and two-tenths hours; duration of secretion, two and seven-tenths days, and time required for cure, three and four-tenths days.

The second patient treated with sulfathiazole (patient 32) was an infant who was born two months prematurely and who weighed only 1,470 Gm. His general condition was poor, and he did not take nourish-

ment well. The respirations were rapid and shallow, and some cyanosis was present. Some doubt was expressed as to whether he would be able to tolerate any of the drugs. Notwithstanding, sulfathiazole was given in a dose of 0.5 Gm. per day. The gonococcic infection was cured in four days, and the use of sulfathiazole was discontinued on the fifth day. The child's general condition improved during this period, and no toxic manifestations of the drug were noted. There were 2 other premature infants in this group, who likewise responded satisfactorily.

An adequate fluid intake was provided in all cases. Careful studies of the urine were made at frequent intervals, and no hematuria or renal suppression was noted. Sulfathiazole crystals were found in the urine of 2 patients. No fever, nausea, vomiting or other toxic signs or symptoms were encountered. The mild cyanosis which was so frequent in the sulfanilamide-treated patients was conspicuously absent.

TABLE 3.—*Results of Treatment with Sulfathiazole*

Patient	Age	Date of Admission	Duration of Infection Prior to Treatment, Days	Smears First Negative, Hours	Duration of Purulent Secretion, Days	Time Required for Cure, Days	Eye Involved		Average Level of Sulfathiazole in Blood, Mg. per 100 Cc.
							Right	Left	
31	5 days.....	7/23/40	2	48	2	4	+	+	4.8
32	Premature..	9/27/40	2	48	3	4	+	+	6.4
33	Premature..	10/20/40	4	18	3	4	+	+	N. D.*
34	6 days.....	11/21/40	2	12	3	3	+	+	6.4
35	3 weeks.....	12/28/40	14	12	2	3	+	+	N. D.*
36	6 weeks.....	1/ 3/41	35	14	3	3	+	+	5.6
37	3 weeks.....	1/18/41	12	36	4	4	+	+	4.6
38	8 days.....	1/24/41	4	14	2	3	+	0	N. D.*
39	9 days.....	1/30/41	5	24	3	3	+	+	8.2
40	Premature..	2/14/41	4	16	2	3	+	+	8.5

* Not determined.

As previously stated, the only adjuvant treatment given was boric acid irrigations. It was necessary to irrigate the cul-de-sac three or four times daily for the first or second day and then only once or twice daily for the remaining two or three days.

In all cases in this group the conjunctiva regained its normal appearance by the end of the period of treatment. There were no corneal complications or relapses. Epithelial smears, which were taken either on the first day or on the second day after the first negative smear of the secretion, did not show any organisms.

COMMENT

A summary of the data on the three therapeutic groups is given in table 4.

The results of treatment with sulfanilamide are in agreement with those of previous reports. In 18 cases cure was effected within eight

days. In 2 cases the condition was refractory. In 1 twenty-eight days of treatment was required, while in the second cure was effected in fourteen days. As previously stated, such refractoriness is fairly common. A probable explanation for the unsuccessful results is that the gonococcus develops a tolerance to sulfanilamide. Boak and Carpenter [62] have demonstrated experimentally that culture of the organism in low concentrations of the drug increases the tolerance of individual strains as high as one hundred times.

The results of treatment with sulfapyridine indicate that it was more effective than sulfanilamide. Also, cyanosis was less frequent. These facts are in agreement with the observations of Michie and Webster,[31] Slobozianu and Herscovici [32] and other observers from abroad, who have expressed the opinion that this compound is preferable to sulfanilamide in the treatment of gonorrheal ophthalmia.

On the basis of this study, sulfathiazole seems to be superior to both sulfanilamide and sulfapyridine. One of the most striking evidences of this was that in 7 cases the gonococci disappeared from the secretion

TABLE 4.—*Summary of Results*

Compound	Number of Cases	First Negative Smear	Duration of Purulent Secretion	Time Required for Cure
Sulfanilamide	20	4.9 days	5.7 days	7.2 days
Sulfapyridine	10	2.4 days	3.7 days	4.8 days
Sulfathiazole	10	24.2 hours	2.7 days	3.4 days

within twelve to twenty-four hours after treatment was instituted. In all cases the swelling and inflammation subsided and the discharge lessened within twelve hours. The average time required for cure was three and four-tenths days, and the maximum time was four days. In this series the use of sulfathiazole was conspicuously unattended by any signs of toxicity.

The opinion that sulfathiazole appears to be the compound of choice for the treatment of gonorrheal ophthalmia is partly substantiated by current reports from urologists who have the opportunity to treat large numbers of gonococcic infections. Cook,[63] in discussing chemotherapy in urology, stated that sulfathiazole is the drug par excellence for the treat-

62. Boak, R. A., and Carpenter, C. M.: Tolerance of Gonococcus in Vitro for Increasing Concentrations of Sulfanilamide, in Gonococcus and Gonococcal Infection, Publication no. 11, American Association for the Advancement of Science, Lancaster, Pa., Science Press, 1939, p. 118.

63. Cook, E. N.: Chemotherapy in Urology, J. A. M. A. **115**:2079 (Dec. 14) 1940.

ment of gonorrhea. Miescher, [64] basing his opinion on a series of 964 cases of genital gonorrhea treated with sulfanilamide and its derivatives, has likewise expressed the opinion that "sulfathiazole appears to be the most effective and best tolerated antigonorrheal preparation."

CONCLUSION

Forty patients with gonorrheal ophthalmia were treated at Clèveland City Hospital from July 1938 to March 1941. Twenty were treated with sulfanilamide, 10 with sulfapyridine and the remainder with sulfathiazole.

Sulfapyridine is more effective than sulfanilamide in the treatment of gonorrheal ophthalmia, but sulfathiazole is superior to both. Sulfathiazole is the compound of choice not only because of its therapeutic efficiency but because of the low incidence of toxic reactions encountered in its use.

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64. Miescher, G.: Der heutige Stand der peroral Chemotherapie der Gonorrhoe auf Grund eigener Erfahrungen (964 Fälle) zugleich Mitteilung über Erfolge mit der schweizer Präparaten "Ciba 3714" und "Cilagen 4", Schweiz. med. Wchnschr. **70**:621 (June 29) 1940.

RETINITIS PIGMENTOSA WITH WIDESPREAD GLIOSIS—SO-CALLED CHOROIDEREMIA

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The term choroideremia was introduced by Mauthner [1] in 1871 to designate a condition which he assumed to exist in a case described by him. From the ophthalmoscopic appearances he assumed that the choroid was completely absent from the fundus everywhere except behind the macula. He stated the belief that the condition was congenital. Under this title many cases have since been reported. In this country Parker and Fralick [2] in 1931 reported what appears to have been a case of true choroideremia. They made the interesting speculation that choroideremia is analogous to coloboma of the macula, assuming that the former condition results when the extramacular, and the latter when the macular, system of choroidal vessels fails to develop. Since, however, choroideremia has never been observed microscopically, it is not certain that the anomaly has ever actually occurred. And even in cases such as that described by Parker and Fralick, the presence of pigment spots similar to those of retinitis pigmentosa raises doubt as to the diagnosis. In addition to proving the existence of true choroideremia, histologic examination of an eye with this condition would answer many interesting questions; for example, is the pigment epithelium present in the affected region and where and how does the uvea begin at the periphery of the fundus?

It has been suggested that choroideremia may occur as the terminal stage of gyrate atrophy of the choroid. Such a transition, however, has never been actually observed. Moreover, since an eye with gyrate atrophy has never been examined microscopically, there is no histologic support for the assumption that this process may lead to complete disappearance of the choroid in an affected area. But even if the choroid around the macula completely disappeared as the result of gyrate atrophy, the terminal condition should be designated acquired choroideremia to distinguish it from the classic conception.

The purpose of the present communication is briefly to present convincing evidence that many cases in which the diagnosis "choroider-

1. Mauthner, L.: Ein Fall von Chorioideremia, Ber. d. naturw.-med. Ver. in Innsbruck **2**:191, 1871; cited by Bedell.[4]

2. Parker, W. R., and Fralick, F. B.: Choroideremia, Tr. Sect. Ophth., A. M. A., 1931, p. 240.

emia" is made are really cases of retinitis pigmentosa in which the choroid is intact but hidden from view by a deep-seated retinal opacity resulting from gliosis. Leber suggested a relationship of choroideremia to retinitis pigmentosa, but I am not aware that he or any other previous observer has expressed even the slightest doubt that the choroid was absent in the areas concerned.

In many cases of retinitis pigmentosa the retina remains everywhere transparent so that, owing no doubt to more or less depigmentation of the pigment epithelium, the choroid is abnormally visible. In many other cases the retina shows areas of gray or white deep-seated opacity. These areas hide the choroid from view and differ in size and number in different cases. Such retinal opacities existed in the case reported by me [3] in 1931, in which I examined one of the eyes histologically. Both eyes were completely blind. The left eye showed a typical picture of retinitis pigmentosa. "In places where there was much pigment the retina showed a deep-seated gray opacity. Except behind these areas, the choroidal vessels were plainly seen." The right eye could not be examined ophthalmoscopically, owing to acute tuberculous iritis which led to its prompt removal at the patient's urgent request. Microscopically, the retina showed areas in which the neuroepithelium was completely replaced by a relatively massive growth of neuroglia (figs. 2 and 4 of Verhoeff [3]). In the other retinal layers the gliosis was slight. Obviously the retinal opacities seen ophthalmoscopically in the left eye were areas of gliosis such as were later seen microscopically in the right.

On the program for the meeting of the New England Ophthalmological Society for March 17, 1936 there was listed a communication entitled "Choroideremia, Dr. J. Herbert Waite." About thirty minutes before the meeting Dr. Waite exhibited to me 3 patients he was to present. The condition of 1 of these patients he had diagnosed choroideremia. The other 2 patients, brothers of the first, he had seen only recently—after he had sent in the title of his communication. The condition of these 2 patients he had diagnosed retinitis pigmentosa. Ophthalmoscopic examination convinced me that his first patient's condition was not choroideremia but retinitis pigmentosa with widespread gliosis. His other 2 patients also had gliosis, but it was much less marked. Dr. Waite accepted my view and presented it at the meeting, making use of a lantern slide (fig. 2 of Verhoeff [3]) with which I provided him.

After this event Dr. Trygve Gundersen discovered a different family, 5 of whose members were affected similarly to Dr. Waite's patients. Two of the 5 members had fundi closely resembling those of Dr. Waite's patient with supposed choroideremia. With the permission of Dr. Gun-

3. Verhoeff, F. H.: Microscopic Observations in a Case of Retinitis Pigmentosa, Arch. Ophth. **5**:392 (March) 1931.

dersen I have examined several of his patients. My reasons for believing that in all the 8 patients the condition was retinitis pigmentosa with more or less widespread gliosis may be briefly summarized as follows:

1. The visual symptoms were those of retinitis pigmentosa.

2. The history in each case indicated that the condition was hereditary but not congenital and was slowly progressive from an early period of life.

3. In only 3 of the 8 cases was the classic conception of choroideremia closely approximated. In the other cases the white opacity occurred in patches more or less scattered.

4. The opacities were not as brilliantly white as a coloboma of the choroid, and they had a fine texture. From a study of their edges it was evident that they did not represent exposed sclera but were deep-seated retinal opacities which obscured the choroid.

5. The obvious explanation for the retinal opacities was retinal gliosis of the degenerated neuroepithelial layer such as I had observed microscopically in retinitis pigmentosa but more massive and widespread.

No doubt some of the cases reported in the literature as cases of choroideremia were really cases of retinitis pigmentosa such as I have just considered, but I shall not here attempt to identify the individual cases. In cases in which the affected region was as white as that of a coloboma of the choroid the condition may really have been choroideremia.

To illustrate the confusion caused by cases of retinitis pigmentosa with widespread gliosis, I may call attention to Bedell's [4] notable communication on the subject of choroideremia. For this the author was awarded the "Lucien Howe prize for ophthalmic research given by the Medical Society of the State of New York." Bedell reviewed many cases recorded in the literature and reported 5 cases of his own. Not one of his cases, however, accorded with Mauthner's conception of choroideremia—in each more or less choroid was visible elsewhere than behind the macula. Moreover, in view of the evidence I have presented, not 1 of his cases can be accepted, even with approximate safety, as a case of true choroideremia. He depicted photographically the fundi in 3 of his cases. As perfectly as it is possible for reproduced photographs to do so, the pictures accord with the ophthalmoscopic appearance of retinitis pigmentosa in which large areas of the choroid are hidden by retinal gliosis. Bedell concluded that "choroideremia is an entity with a pathognomonic fundus, and as it develops during the life of the patient it must not be considered as a congenital absence of the choroid but as a

4. Bedell, A. J.: Choroideremia, Arch. Ophth. **7**:444 (March) 1937.

dissolution of that membrane." He discussed choroidal sclerosis but left the question open as to whether this is the cause of choroideremia. In this connection I may state my belief that a diagnosis of sclerosis of the choroidal vessels is often made on insufficient evidence. It has not been demonstrated that choroidal vessels masked by white streaks necessarily have abnormal walls or lumens.

Since in retinitis pigmentosa retinal opacities vary greatly in size and number in different cases, it is not surprising that in unusual cases the whole retina with the exception of the macula should be opacified. The macula escapes because its neuroepithelium degenerates very late. Why it is that retinal gliosis should thus vary in degree, and in many cases apparently be entirely lacking, I do not know. Possibly it is influenced by hereditary factors not necessarily associated with those of retinitis pigmentosa. In this connection it is to be noted that in almost all, if not all, the cases of "choroideremia" reported in the literature the patient has been male. In striking agreement with this are the facts that all 3 of Dr. Waite's patients were male and that of Dr. Gundersen's 5 patients the 2 whose fundus lesions closely approximated the classic conception of choroideremia were male, while the others were female. It would seem, therefore, that in cases of retinitis pigmentosa a tendency toward widespread gliosis is a male characteristic.

CONCLUSIONS

True choroideremia, according to the classic conception of this condition, probably occurs, but some doubt as to its occurrence must exist until it has been demonstrated histologically.

Many cases of supposed choroideremia are really cases of retinitis pigmentosa in which the choroid is hidden by widespread gliosis of the degenerated neuroepithelial layer of the retina. In rare cases the gliosis involves the whole extent of the retina with the exception of the macula. In such cases the condition may be termed pseudochoroideremia.

395 Commonwealth Avenue.

CRYSTALLINE DYSTROPHY OF THE CORNEA

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Crystalline deposits in the cornea have infrequently been described in ophthalmic literature. They have been observed secondary to trachoma, chronic iritis, operative wounds and other lesions. More rarely they constitute or are part of the primary lesion in the eye. Vogt,[1] under the heading "Parenchymatous Crystalline Degeneration of the Cornea," included in his atlas several cases, most of which were probably of lesions of the secondary type. He stated that the condition has, among others, the following characteristics: unilaterality, slight or no vascularization, freedom from inflammation, involvement of the deeper layers and a dense opacity. Other cases, probably to be classed as of lesions of this type, have been reported by Beck,[2] Schuster,[3] Ulbrich,[4] Bachstez,[5] Kusama,[6] Meyer [7] and Pillat.[8]

Uhthoff [9] observed for many years a patient with frequently recurring attacks of moderately severe episcleral redness in both eyes, in each of which there eventually appeared a ring-shaped peripheral opacity containing countless crystals. Examination of an excised piece of the opaque portion showed that they were uric acid and sodium urate.

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1. Vogt, A.: Lehrbuch und Atlas der Spaltlampenmikroscopie des lebenden Auges, Berlin, Julius Springer, 1930, p. 125.

2. Beck, A.: Zur Casuistik krystallähnlicher Gebilde der Hornhaut, Arch. f. Augenh. **55**:285, 1906.

3. Schuster, P.: Zur Casuistik krystallähnlicher Gebilde des Auges, Arch. f. Augenh. **54**:363, 1906.

4. Ulbrich, H.: Durchsetzung der Hornhaut mit einer Unzahl feinster glitzernder Pünktchen, Klin. Monatsbl. f. Augenh. **52**:289, 1914.

5. Bachstez, E.: Ueber Verfettung in der Hornhaut, Arch. f. Ophth. **105**: 997, 1921.

6. Kusama: Ein Beitrag zur primären fettigen Degeneration der Kornea, Klin. Monatsbl. f. Augenh. **66**:111, 1921.

7. Meyer, H.: Beitrag zum Krankheitsbild der Dystrophia adiposa Corneae, Klin. Monatsbl. f. Augenh. **81**:786, 1928.

8. Pillat, A.: Kristallinische Hornhautentartung, Ztschr. f. Augenh. **82**:325, 1934.

9. Uhthoff, W.: Doppelseitige symmetrische Degeneration der Kornea, mit Ablagerungen von Harnsäure und saurem, harnsaurem Natron bei sonst normaler Beschaffenheit der Augen und gutem Allgemeinbefinden, Klin. Monatsbl. f. Augenh. **54**:383, 1915.

A case of primary cholesterinemic infiltration of the cornea in a 19 year old girl has been described by Toth [10]; recurrent attacks of redness of both eyes had been present since the age of 8 years. A gray 0.5 mm. wide opacity like an arcus senilis was present. In the cornea of one eye between the 6 and the 10 o'clock position was a structure 1.5 mm. wide containing a mass of crystals. The blood cholesterol content was 312 mg. per hundred cubic centimeters.

Familial degeneration of the cornea associated with crystalline deposits has been observed by von Hippel,[11] Tritscheller,[12] van Wendt and Wibaut [13] and Schnyder.[14] The patients have all shown localized and usually disk-shaped opacities containing crystals.

I have had the opportunity of observing a patient with an unusual and striking corneal lesion which cannot be classified as belonging to any of the types mentioned, since it consisted entirely of crystals, was not associated with any scar or other opacity or with any inflammatory process and occupied the entire anterior third of the cornea rather than being localized.

The patient, A. H., a white man with presbyopic symptoms, was first examined Jan. 23, 1936, at the age of 45. The vision in each eye with correction for a small amount of compound hyperopic astigmatism was 20/20. Examination of the conjunctiva, anterior chamber, iris, media and fundus of each eye gave negative results. The cornea of each eye showed a faint suggestion of a haze when examined with the Berger loupe. Examination with the slit lamp microscope showed this effect to be the result of the presence of countless minute crystals lying in the anterior portion of the cornea, densely packed in and beneath Bowman's membrane and more sparsely distributed through the remaining anterior third of the cornea. They extended from limbus to limbus in all directions, although slightly less dense in the periphery than elsewhere, and in the light of the slit lamp glistened brilliantly, showing many colors—red, green, blue and gold—and resembling nothing so much as finely ground iridescent glass or tinsel. With the ocular micrometer in the microscope they measured 0.02 to 0.05 mm.

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10. Toth, Z.: Ein Fall von primärer, annulärer, cholesterinämischer Infiltration der Kornea, Klin. Monatsbl. f. Augenh. **91**:502, 1933.

11. von Hippel: Eine noch nicht beschriebene Form von erblicher degenerativer Hornhauterkrankung, Klin. Monatsbl. f. Augenh. **83**:115, 1929.

12. Tritscheller: Beitrag zur Vererbung der familiären Hornhautentartung, Klin. Monatsbl. f. Augenh. **66**:579, 1921.

13. van Wendt and Wibaut, cited by Waardenburg, P. J.: Das menschliche Auge und seine Erbanlagen, The Hague, Martinus Nijhoff, 1932.

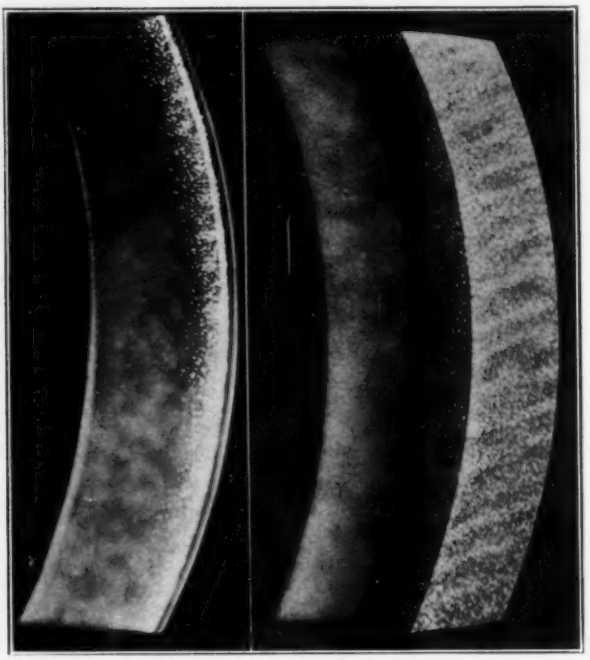
14. Schnyder: Scheibenförmige Kristalleinlagerungen in der Hornhautmitte als Erbleiden, Klin. Monatsbl. f. Augenh. **103**:494, 1939.

General physical examination revealed nothing abnormal. Examination of the urine gave negative results, as did a blood count and a Wassermann examination of the blood. The blood cholesterol content was 167 mg. and the blood uric acid content 3.4 mg. per hundred cubic centimeters.

Examination of the eyes of the patient's three children and of his brother, the only relatives available for examination, was negative for any similar condition.

The patient was examined again in 1937, 1940 and 1941 and showed no change except an increase of his presbyopia.

Nothing in the patient's history or in the findings gives any hint as to the origin or the nature of his corneal lesion. There has been no



Slit lamp appearance of the cornea, showing the location and distribution of the crystals.

change in five years, and therefore one can hardly—especially since there are no corneal opacities—consider the condition a degeneration. It seems only reasonable to assume that it is congenital and to be classed as a dystrophy. The crystals have the brilliant coloring of the cholesterol crystals sometimes seen in the anterior chamber, but they do not appear as large, although this impression may be the result of the magnification produced by the cornea itself when one looks through it into the anterior chamber. It is unfortunate that more members of the family cannot

be examined in order to establish a possible hereditary factor, which may well be present.

SUMMARY

An apparently hitherto unreported corneal dystrophy is described. It consists of countless varicolored microscopic crystals, resembling cholesterol, distributed throughout the anterior portion of the cornea. There are no opacities, inflammatory signs or visual disturbances.

671 Broad Street.

THE CORNEA

II. TRANSFER OF WATER AND SODIUM CHLORIDE BY HYDROSTATIC PRESSURE THROUGH THE EXCISED CORNEA

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V. EVERETT KINSEY, PH.D.
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The potential forces affecting the transfer of water and dissolved substances through the cornea are osmosis, diffusion and hydrostatic pressure. It is the purpose of this and the preceding paper [1] of this series to report the effect of these forces on the excised cornea. While the experimental results should not be unqualifiedly applied to the conditions in vivo, it is our belief that the different factors can be separately evaluated only in the relatively simple in vitro preparations. Previously we have reported the effect of diffusion and that special instance of diffusion, osmosis, for the transfer of water and sodium chloride through the excised cornea.

Our objectives in the present study are threefold: (1) to compare the amounts of fluid transferred by a given hydrostatic pressure through the cornea before and after removal of its constituent membranes; (2) to compare the amount of fluid transferred through the intact cornea, employing different hydrostatic pressures and (3) to determine the osmotic equivalent of a given hydrostatic pressure. The first should enable one to allocate specific barrier properties to the individual layers of the cornea; the second should provide information on the effect of pressure per se on the amount of fluid transferred, and the third should enable one to obtain a quantitative index of the degree of semipermeability of the cornea.

There have been remarkably few studies made on the effectiveness of hydrostatic pressure in forcing fluid through the cornea. Prior to Leber's [2] report in 1873 it was thought that the aqueous continually

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From the Harvard Medical School and the Howe Laboratory of Ophthalmology.

1. Cogan, D. G., and Kinsey, V. E.: The Cornea: I. Transfer of Water and Sodium Chloride by Osmosis and Diffusion Through the Excised Cornea, Arch. Ophth. **27**:466 (March) 1942.

2. Leber, T.: Studien über der Flüssigkeitswechsel im Auge, Arch. f. Ophth. (pt. 2) **19**:87-186, 1873.

passes outward through small pores in the cornea. This idea was based on the observation that continued compression of the eye caused small droplets to appear on the surface of the cornea. Leber denied that such a transfer of fluid occurs normally and pointed to the fact that the cornea of a proptosed rabbit eye did not remain moist, as it would, he stated, if aqueous were coming through the cornea. To determine what pressure is needed to force fluid through the cornea, Leber performed the following experiment: Rabbit corneas were tied onto the ends of tubes, and the tubes were filled with 0.75 per cent sodium chloride solution or distilled water. Various pressures were exerted on the fluid in the tubes while the surfaces of the corneas, which were exposed to the air, were observed grossly during a two hour period for any increase in dampness or for droplets. Leber reported that only when a pressure of at least 200 mm. of mercury was used did fluid come through the intact cornea. He concluded, therefore, that any hydrostatic pressure which may exist in a normal eye is insufficient to force fluid through the cornea. The real barrier to the transfer of fluid through the normal cornea is, according to Leber, the endothelium, for removal of the endothelium causes the cornea to swell, presumably from unobstructed imbibition of aqueous.

More recently Ridley,[3] in a study of ocular fluid exchange, presented data on the transfer of artificial aqueous through the cornea into artificial tears with a pressure of 25 and of 50 mm. of mercury. But, as there was an osmotic pressure simultaneously operative as well as an undetermined amount of stretching, his figures do not indicate the effect of hydrostatic pressure alone.

A partial view of the apparatus employed in all the present experiments on hydrostatic pressure is shown in figure 1. The source of pressure was a commercial tank of compressed air, which was connected with a 20 liter reserve bottle, a mercury manometer and a hollow rod on the under side of which were twenty tubular outlets. During the experiment these outlets were connected by means of rubber tubing with the pipets that held the corneas. The corneas were prepared and attached to the pipets in a manner similar to that previously employed for experiments with osmosis and diffusion. Again it was impossible to obtain excised corneas without damaging the endothelium, and any effect resulting from the removal of endothelium and of Descemet's membrane is difficult to assess quantitatively. After the corneas were fastened, the tubes were partly filled with the test fluid and attached to the outlets.

3. Ridley, F.: An Experimental Investigation into the Intraocular Pressure and Drainage of the Aqueous Humor: Part I, Tr. Ophth. Soc. U. Kingdom **50**: 268-309, 1930.

Any desired head of pressure on the fluid in the pipets could be obtained by means of a regulating valve on the tank. Any additional change in fluid level was then a measure of the transfer of fluid through the cornea.

For most of the experiments 4 cc. of 1 per cent sodium chloride solution was placed in each pipet and 10 cc. of the same solution in the flasks. Changes in the level of fluid in the pipets were recorded at various intervals. As in the previously reported experiments, no attempt was made to control the hydrogen ion concentration, although this was measured electrometrically before and after the experiments. Again it was found that when the solutions were placed in contact with the cornea they assumed a p_H of approximately 6.5.

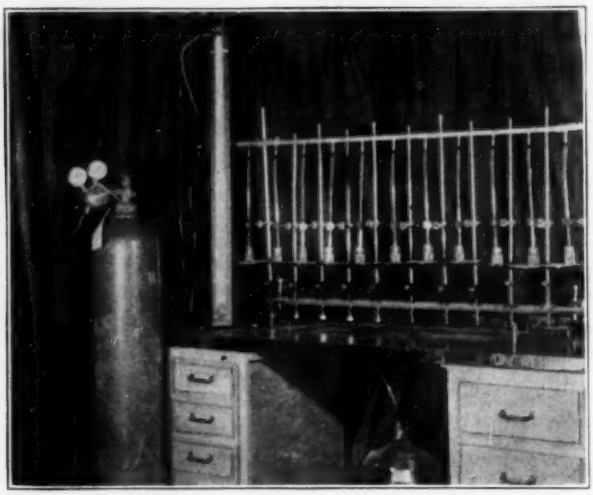

Fig. 1.—Partial view of the apparatus used for the hydrostatic pressure experiments.

I. TRANSFER OF FLUID THROUGH THE WHOLE CORNEA AND THROUGH THE CORNEA FROM WHICH VARIOUS LAYERS HAD BEEN REMOVED

For these experiments a pressure of 100 mm. of mercury was used.

The transfer of fluid through the whole cornea and through the cornea from which the various membranes had been removed is indicated for the out-in direction in figure 2 and for the in-out direction in figure 3. Each point on the graphs represents an average of 7 to 9 separate experiments. All the values are high by an amount equivalent to the stretching of the cornea. This stretching, which increased progressively throughout the period of observation and could be measured by manually replacing the cornea to its original position, was found to correspond to approximately 0.1 cc. at the end of the experiment.

In the out-in direction (fig. 2) little or no fluid is transferred so long as the epithelium is present (*A, C*), while after the removal of the epithelium there is considerable transfer of fluid (*B, D*) under otherwise identical conditions. What effect the endothelium and Descemet's mem-

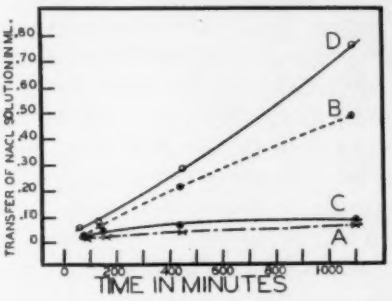

Fig. 2.—Average quantity (each point represents 7 to 9 experiments) of 1 per cent sodium chloride solution transferred through the cornea in an out-in direction by a hydrostatic pressure of 100 mm. of mercury. *A*, cornea intact; *B*, epithelium removed; *C*, endothelium and Descemet's membrane removed, and *D*, epithelium, endothelium and Descemet's membrane removed.

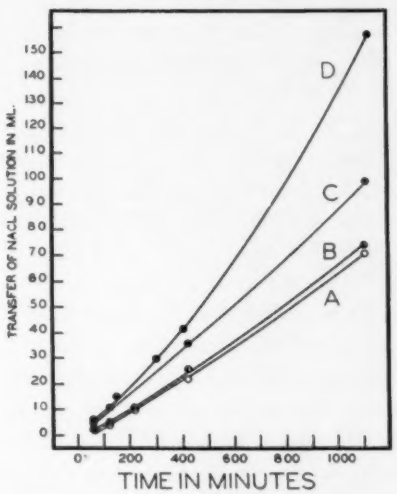

Fig. 3.—Average quantity (each point represents 7 to 9 experiments) of 1 per cent sodium chloride solution transferred through the cornea in an in-out direction by a pressure of 100 mm. of mercury. *A*, cornea intact; *B*, epithelium removed; *C*, endothelium and Descemet's membrane removed, and *D*, epithelium, endothelium and Descemet's membrane removed.

brane may have on the transfer of fluid is masked in *A* and *C* by the presence of the epithelium, so that removal of the endothelium and Descemet's membrane appears to be without effect. If the endothelium

and Descemet's membrane are removed, however, along with the epithelium, the amount of fluid transferred is seen to be considerably greater (*D*) than when epithelium alone is removed (*B*). Hence the endothelium and Descemet's membrane even though partially damaged are apparently capable of offering some resistance to the passage of fluid in the direction out-in.

In the in-out direction (fig. 3) there appears to be no marked obstruction to the transfer of fluid by the presence of the epithelium (*A*), for its removal is essentially without effect (*B*). After the removal of the endothelium and Descemet's membrane a greater transfer of fluid was found (*C*). A still greater transfer occurred when the epithelium, the endothelium and Descemet's membrane were removed together (*D*). It is not apparent why the removal of the epithelium, which previously seemed to be without effect, increased the amount of fluid transferred under this circumstance.

In comparing the results shown in figures 2 and 3 it is not remarkable to find that the epithelium prevents the passage of sodium chloride solution in the out-in direction (fig. 2, *A*), for we have previously found the epithelium to be practically impermeable to sodium chloride,[1] and any water transferred would create an opposing osmotic force by changing the sodium chloride concentration on the two sides of the membrane. It may seem unusual, however, that the salt solution appears to pass through the whole cornea in the reverse direction (fig. 3, *A*). It will be remembered that a similarly apparent unidirectional permeability was noted when the transfer of fluid by osmosis was being investigated. Again the explanation undoubtedly lies in the fact that the epithelium is damaged. In the present instance epithelial damage occurred progressively when the hydrostatic pressure was exerted in the in-out direction. Bullae were grossly visible in about 400 minutes with a pressure of 100 mm. of mercury. These were grossly unlike those previously observed with osmotic pressures in that they appeared more transparent and did not coalesce to form large solitary bullae. Nevertheless, the epithelium was severely damaged, and after about 700 minutes it frequently hung down in shreds from the margin of the cornea.

Histologically, swelling of the epithelial cells was detectable in 60 minutes; this progressed slowly for about 350 to 400 minutes. By this time a few small bullae were grossly visible and the epithelial cells were considerably swollen. The entire epithelium was somewhat loosened, and ultimately it was seen to separate spontaneously from the stroma. When distilled water instead of 1 per cent sodium chloride solution was employed the changes were more rapid, bullae usually appearing in about 60 minutes and spontaneous separation of the epithelium within 200 minutes.

In the reverse direction, i. e. out-in, with a pressure of 100 mm. of mercury the epithelium remained practically normal even after 1,100

minutes so long as 1 per cent sodium chloride solution was used. With distilled water the superficial cells were considerably swollen and macerated after 1,100 minutes.

In these experiments it was found that no change in the salt concentration of the fluid in the flasks occurred; that is, sodium chloride and water passed through the cornea either together or not at all. An attempt was made to study separately corneal permeability to water with hydrostatic pressure by employing the procedure described but substituting distilled water for 1 per cent sodium chloride solution. The results are indicated in the accompanying table, in which the amount of fluid transferred at the end of 1,100 minutes is recorded. A correction for stretching the cornea was made, 0.1 cc. having been subtracted from all measurements.

In the experiments with distilled water, as in those with sodium chloride solutions, no appreciable transfer of fluid occurred in the direc-

Average Amount of Fluid (Initially Distilled Water) Transferred Through the Cornea in 1,100 Minutes with a Hydrostatic Pressure of 100 Mm. of Mercury

Corneal Status	Intact	Epithelium Removed	Endothelium and Descemet's Membrane Removed	Substantia Propria Only
Out-in direction	0.03	0.80	−0.03	0.75
	(3)*	(8)	(2)	(13)
In-out direction	0.61	0.64	0.78	0.81
	(3)	(8)	(5)	(17)

* Number of cases.

tion out-in so long as the epithelium was present. Although this result was not anticipated for the experiments with water, in view of our earlier finding that the cornea is freely permeable in both directions to water, it must be remembered that the distilled water soon becomes contaminated by salt eluted from the cornea; in the absence of stirring this salt would form an appreciable concentration next to the cornea.

II. TRANSFER OF FLUID WITH VARIOUS HYDROSTATIC PRESSURES

The effect of pressure on the transfer of fluid through the cornea was investigated with different hydrostatic forces. The technic differed from that in the foregoing experiments in that various pressures were used and the transfer was studied for the whole corneas only. The average results for the in-out direction are indicated in figure 4. Each curve represents a different pressure and is the average of 7 to 9 experiments. The pressures indicated represent the sum of the pressure in the system and that due to the column of liquid in the tube. No measurable exchange of fluid occurred in the reverse direction even with 400 mm. of mercury.

From the graph it may be seen that: (1) the amount of fluid transferred is directly proportional to the hydrostatic pressure; (2) there is some increase in the rate of fluid transferred with time, and (3) the net amount of fluid transferred by physiologically significant hydrostatic pressures is small, amounting to not more than 0.3 cc. in eighteen hours.

III. DETERMINATION OF THE OSMOTIC EQUIVALENT OF A GIVEN HYDROSTATIC PRESSURE

In the following experiments the osmotic equivalent of a given hydrostatic pressure was determined, and a quantitative index of the semipermeability of the cornea was thereby obtained.

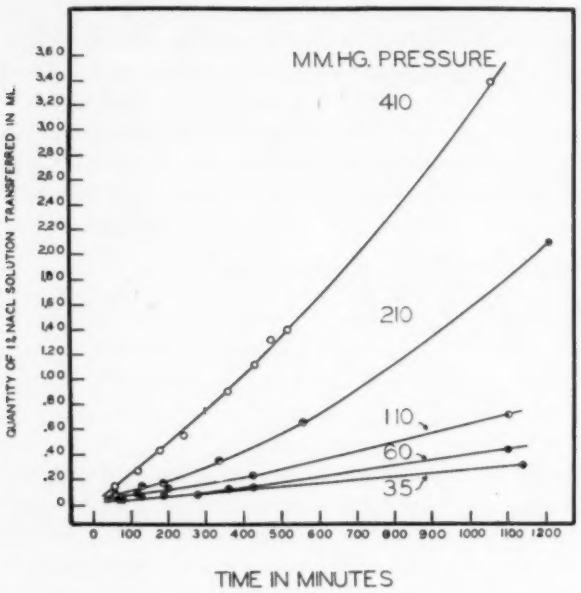

Fig. 4.—Average quantity (each point represents 7 to 9 experiments) of water transferred through the cornea in an in-out direction by various hydrostatic pressures. (No net transfer of water occurred in the reverse direction under similar conditions.)

Whole corneas, all with the epithelial side up, were tied onto the pipets so that the hydrostatic pressure, which was arbitrarily chosen as 400 mm. of mercury, was exerted in the direction out-in. The osmotic pressures used in making the comparison were obtained by placing 1.000 per cent sodium chloride solution in the flasks and sodium chloride solutions of the following percentage concentrations in the pipets: 1.000, 1.005, 1.007, 1.015, 1.030, 1.080, 1.150 and 1.250. All tests were made in triplicate. It is apparent that in this manner the hydrostatic pres-

sure is exerted downward and opposes the osmotic pressure, which is exerted upward. Accordingly, whenever the hydrostatic pressure exceeded the osmotic pressure, the level of fluid in the tube would remain practically stationary, as was previously noted for whole corneas when the hydrostatic pressure was exerted in this direction. On the other hand, when the osmotic pressure exceeded the hydrostatic pressure the level of fluid in the tube would rise.

In figure 5 the *differences* in salt concentration (osmotic pressure) are plotted against the amount of water transferred. A correction was made to compensate for the stretching of the corneas. With concentration differences of 0.03 per cent or less, little or no water is transferred, but with concentration differences greater than 0.03 per cent there is a nearly linear increase in the amount of water transferred. The osmotic equivalent for a hydrostatic pressure of 400 mm. mercury can be taken

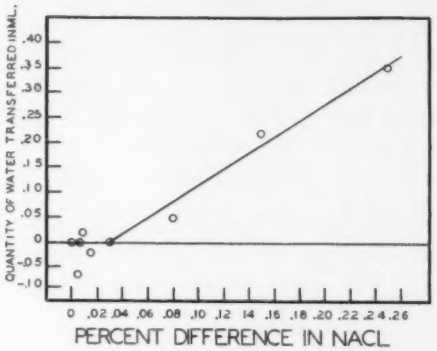

Fig. 5.—Average quantity (each point represents 3 experiments) of water transferred through the cornea in an in-out direction by the osmotic pressure produced by the sodium chloride concentrations shown when opposed by a hydrostatic pressure of 400 mm. of mercury. The time in all cases was 1,100 minutes.

as that point at which the plotted line intersects the zero line. In the present instance this is found to lie between 0.02 and 0.04 per cent. Theoretically the osmotic equivalent of 400 mm. of mercury for a perfect semipermeable membrane is approximately 0.007 per cent sodium chloride solution. It thus appears that the corneal epithelium, for a biologic membrane, possesses a high degree of semipermeability.

COMMENT

In the previously reported experiments on diffusion, it was found that no sodium chloride was transferred through the normal epithelium and that an apparent unidirectionality in permeability of the cornea for sodium chloride in the in-out direction was due to epithelial damage.[1] The present experiments indicate that epithelial damage similarly occurs

in the in-out direction when hydrostatic pressure is used and thereby accounts for the apparent unidirectionality under this condition. It is obvious that any conclusions regarding unidirectional permeability of such membranes as the cornea must take into account the coexistence of damage. It is interesting to note in this connection that the frequently reported unidirectional permeability of frog skin has also been partially attributed by some authors to damage to the epidermis.[4]

By determining the osmotic equivalents for hydrostatic pressure it was found that the cornea is capable of acting as a good semipermeable membrane for sodium chloride. It is, for instance, much more efficient than the isolated frog skin, for which Adolph [5] has shown that an osmotic equivalent of 2.5 per cent sodium chloride solution is required to counterbalance a hydrostatic pressure of but 15 mm. of mercury. It is also noteworthy that despite the histologic similarity of the epithelium of conjunctiva and of cornea, we have found that the excised conjunctiva does not function appreciably as a semipermeable membrane with sodium chloride. This finding of a differential permeability for cornea and conjunctiva has obvious clinical implications with regard to the absorption of therapeutic agents; this will be considered in a subsequent communication.

CONCLUSIONS

1. The excised cornea is impermeable to 1 per cent sodium chloride solution in the out-in direction with hydrostatic pressures up to at least 400 mm. of mercury; this impermeability depends on the integrity of the epithelium.

2. The excised cornea is permeable to 1 per cent sodium chloride solution in the in-out direction under various hydrostatic pressures; this permeability undoubtedly depends on the epithelial damage resulting from the hydrostatic pressure.

3. The amount of fluid when transferred through the cornea is directly proportional to the hydrostatic pressures employed.

4. The corneal epithelium, for a biologic membrane, possesses a high degree of semipermeability with respect to sodium chloride solutions.

Miss Sally Walker and Miss Cynthia Steitz gave technical assistance in these investigations.

243 Charles Street.

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4. Bauer, V.: Die Froschhaut als Organ der Wasserresorption, Arch. f. d. ges. Physiol. **209**:301-332, 1925. Rubinstein, D. L., and Miskinowa, T.: Untersuchungen über einseitige Permeabilität: I. Ist die Froschhaut für Wasser einseitig permeabel? Protoplasma **25**:56-68, 1936.

5. Adolph, E. F.: The Passage of Water Through the Skin of the Frog and the Relation Between Diffusion and Permeability, Am. J. Physiol. **73**:85-105, 1925.

LOCAL USE OF SULFANILAMIDE AND DERIVATIVES IN PRACTICE OF OPHTHALMOLOGY

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The therapeutic value of sulfanilamide and its derivatives is now an established fact. The brilliant clinical results obtained by oral and intravenous administration of these drugs prompted this investigation as to their value when used locally in the treatment of ocular diseases. Kolmer [1] pointed out the efficacy of sulfanilamide crystals (applied locally) in the prevention and the treatment of infections of superficial wounds. Recently Luo and P'an [2] demonstrated that the concentration of sulfanilamide in the aqueous humor is considerably greater after local use of powdered sulfanilamide than after oral administration of large doses of the drug or after local use of the drug in liquid form.

Azosulfamide was the first member of the drug group used by us locally in the eye. It was first available in a 2.5 per cent solution and was instilled into the eye in the treatment of various kinds of acute conjunctivitis and corneal ulcerations. When it is instilled into the eye a mild burning sensation is experienced by the patient, but the inflammatory reaction is slight. The results obtained in acute infections of streptococcic origin were unsatisfactory. We have discontinued its use except for staining corneal lesions. For this purpose it may replace fluorescein or mercurochrome.

Sulfanilamide has great value when applied locally. As the powder produces some pain, a local anesthetic should be instilled preliminary to its use. Favorable clinical results have been obtained in lacerated wounds of the eyelids (after cleansing, the powder is instilled and primary closure done), streptococcic conjunctivitis, streptococcic corneal ulceration and trachoma. For corneal ulceration the drug is applied directly to the lesion with a small spatula.

From the ophthalmologic services of St. Joseph and Research hospitals.

1. Kolmer, J. A.: The Science of Chemotherapy, Arch. Otolaryng. **34**:1-6 (July) 1941.

2. Luo, T. H., and P'an, S. Y.: Concentration of Sulfanilamide in the Aqueous Humor of Human Eyes, with Special Reference to Local Application, Chinese M. J. **58**:167-176 (Aug.) 1940.

Use of sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) powder in the treatment of pneumococcic infections was begun as soon as this drug became available. Satisfactory healing of pneumococcic conjunctivitis and ulcus serpens occurred. Sulfapyridine causes more discomfort than either sulfanilamide or sulfathiazole.

Sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) is the member of the group most valuable to the ophthalmologist as a local medicament. Prepared in ointment form it is valuable in the treatment of perifolliculitis, blepharitis squamosa and blepharitis ulcerosa. A 25 per cent concentration of sulfathiazole in an oxycholesterol-petrolatum ointment base is recommended. For pneumococcic and staphylococcic infections of the conjunctiva and the cornea, the powdered form is better. This may be dusted in with a camel's hair brush, applied with a cotton swab or gently blown onto the eyeball with an insufflator.

The local use of these drugs in the eye should in no way interfere with oral or intravenous administration. Local application does not materially affect the level in the blood; therefore the two methods may be used simultaneously without fear of untoward results.

Although little is known concerning the local physiologic and therapeutic action of sulfanilamide and its derivatives, the clinical results obtained justify their use in the treatment of certain diseases of the eye.

607 Commerce Trust Building.

DEVIC'S DISEASE (OPHTHALMONEUROMYELITIS)

A CLINICOPATHOLOGIC STUDY

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Ophthalmoneuromyelitis, or Devic's disease, was first described by Devic [1] as an entity in 1894. It is characterized by a disease process that is relatively afebrile and strictly limited to the spinal cord and optic nerves. Because of the distribution of the lesions, the reports of this syndrome have found their way into both the neurologic and the ophthalmologic literature, primarily the latter. In the more recent literature there has been a tendency to interpret the syndrome loosely, and cases of almost any type of involvement of the central nervous system associated with a disturbance of the optic nerves have been reported as instances of Devic's disease. Because of this loose interpretation, the clinical syndrome has gradually lost many of its original characteristics. An actual discussion would, therefore, require first a most careful sifting of the literature in an attempt to eliminate the less accurately defined and the less definite cases. When this is done one finds that the literature on the disease is not extensive. Therefore, we feel that there would be definite value in a detailed report of the clinicopathologic observations in a fairly typical case as well as in an attempt to summarize some of the more characteristic features of the syndrome.

In the literature this condition has been described as a rare neurologic syndrome of optic neuritis and myelitis. It has frequently been called optic neuromyelitis, ophthalmoneuromyelitis, neuroptic myelitis or Devic's disease. Balser [2] found 110 cases in the literature which he believed conformed to the criteria of the syndrome. He believed, as did others (Walsh,[3] Hassin [4]), that the condition is a distinct disease entity

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1. Devic, E.: Myélite subaiguë compliquée de névrite optique, Bull. méd. **8**: 1033, 1894.

2. Balser, B. H.: Neuromyelitis Optica, Brain **59**:353, 1936.

3. Walsh, F. R.: Neuromyelitis Optica, Bull. Johns Hopkins Hosp. **56**:183, 1935.

4. Hassin, G. B.: Neuroptic Myelitis Versus Multiple Sclerosis, Arch. Neurol. & Psychiat. **37**:1083 (May) 1937.

rather than a clinical syndrome. On the other hand, Ferraro [5] maintained that ophthalmoneuromyelitis is merely a variety of acute multiple sclerosis or disseminated encephalomyelitis. All authorities agree that it is a nonvascular, degenerative condition whose etiology is still obscure.

CLINICAL PICTURE

The outstanding clinical feature is bilateral blindness associated with the symptoms of myelitis. The onset is usually acute and may be introduced by either visual or myelitic symptoms. Perritt [6] observed patients with complete amaurosis in whom vision had returned while the myelitis was still progressing.

The myelitis is diffuse, disseminated or ascending. Sensory disturbances often precede the motor findings. The initial complaint frequently consists of lumbar pain or of paresthesias in the lower extremities, followed rapidly by hypesthesia or even complete anesthesia. The sensory loss is commonly symmetric, producing a definite sensory level. One of Sequin's [7] patients presented a Brown-Séquard hemisection of the cord. The motor involvement varies from paresis to complete paralysis. Disturbances of the bladder occur in the cases of advanced involvement.

Both optic nerves are usually affected, although involvement in one eye sometimes precedes that in the other by a few days or weeks. The visual loss becomes pronounced and often complete. Visual field defects may assume any pattern, the most common being characterized by a bilateral central scotoma. Central blindness is extremely rare. In the early stages the optic nerve head not infrequently appears normal, but later it may reveal progressive atrophy. Occasionally there occurs optic neuritis with a mild elevation of the papilla.

The spinal fluid is either normal or reveals mild pleocytosis. Balser [2] found the cells to be both polymorphonuclear and mononuclear leukocytes. An atypical gold curve and increased pressure are sometimes noted.

In contrast to some of the supposedly related conditions, such as multiple sclerosis, this disease exempts no age and neither sex.

The literature contains many cases reported as instances of Devic's disease in which there has been complete recovery. However, in view of the laxity of the use of this term and in view of the severity of the pathologic lesions in the fatal cases, one is forced at present to be less optimistic when considering the final prognosis in this syndrome. The course is frequently rapid, ranging from a few months to a few years. Death is usually due to pneumonia, urinary infection or involvement of

5. Ferraro, A.: Primary Demyelinating Processes of the Central Nervous System, Arch. Neurol. & Psychiat. **37**:1100 (May) 1937.

6. Perritt, R. A.: Optic Neuromyelitis, Arch. Ophth. **11**:492 (March) 1934.

7. Sequin, E. C.: On the Coincidence of Optic Neuritis and Subacute Transverse Myelitis, J. Nerv. & Ment. Dis. **7**:177, 1880.

the respiratory tract secondary to the ascending damage to the cord. In many of the nonfatal cases the syndrome is followed by permanent neurologic sequels, although complete remissions have been reported.

PATHOLOGY

Pathologic examination usually reveals ample lesions to account for the neurologic symptoms. Sections of the cord show macroscopic necrosis and cavitation. The optic nerves, the chiasm or the tracts frequently are grossly atrophic.

The characteristic histopathologic feature of this disease is the resultant necrosis without significant glial repair. There is a marked destruction of the parenchyma of the spinal cord involving the central gray substance as well as the white matter. The destroyed areas are usually occupied by large numbers of microglia, rod cells, fat granule cells and newly formed blood vessels. The lesions are not well demarcated but gradually fuse with the adjacent parenchyma, which reveals swollen and altered myelin sheaths. The ganglion cells of the intact anterior horns contain various alterations, such as swelling, chromatolysis, neurofibrillary dissolution, vacuolization, nuclear changes, cell shrinkage and ghost cell formation. In the advanced lesions many of the axis cylinders are fragmented, destroyed and finally engulfed by scavenger cells. The remaining axons reveal tinctorial loss, irregular swelling and end bulb formation. There is commonly a moderate proliferation of astrocytes which show degenerative alterations, such as clasmatodendrosis and ameboid cell formation. Proliferation of astroglial fibers occurs only in the older lesions and is never pronounced. Complete glial repair by the formation of a glial scar does not occur. Proliferation of the connective tissue of the vascular adventitia is sometimes seen in older lesions. A perivascular inflammatory infiltrate involving the small vessels occurs both within and between the areas of destruction. The cells are usually mononuclear or plasma cells. However, Balser [2] encountered many polymorphonuclear leukocytes in the perivascular exudate in his cases. The spinal rootlets sometimes contain degenerative changes. Walsh [3] found the dorsal rootlets involved more often than the ventral. Moreover, the only rootlets involved were those in segments of the cord showing the most profound necrosis.

The optic nerves, the chiasm or the tracts present the same histologic changes as the cord. Myelin alterations may occur in the cerebrum, especially in the calcarine cortex, but are visible only microscopically.

REPORT OF A CASE

Mrs. M. P., aged 48, was admitted to the University Hospital on Sept. 13, 1940. Her illness had begun one and one-half years before admission, with a rapid onset of total bilateral amaurosis; the blindness lasted five days and gradually

improved, although the visual acuity never returned to normal. Blindness again occurred six months later. At this time the patient experienced for the first time a numbness of the distal portions of the lower extremities, which slowly proceeded centrally to produce eventually a complete sensory loss to the level of the fifth dorsal segment. She also noted some paresis of both lower extremities, which became pronounced within seven days. After the persistence of this paralysis for almost half a year, improvement began, and within a few months the patient was able to get out of bed and walk fairly well. There occurred a slight concomitant return of vision, which enabled her to recognize large objects when they were held close to her eyes. This improvement continued for three months. One month before her admission to the hospital numbness in her feet returned, and in about one week she again had a complete motor and sensory involvement of her lower limbs. She was unable to urinate and suffered marked constipation.

Examination at the time of her admission revealed a blood pressure of 100 systolic and 80 diastolic; her nutrition was fair. There was a shallow decubitus over the sacrum. The neurologic examination disclosed total bilateral blindness due to optic nerve atrophy. The pupils were large and did not react to light. Nystagmus was noted on lateral gaze. The biceps and the triceps reflex were depressed. The abdominal reflexes and the knee and ankle jerks were absent, as was the Babinski sign. A spinal reflex was elicited, however, by stroking the plantar surfaces of each foot. There was a complete sensory loss extending to the level of the fourth thoracic segment and also complete flaccid paralysis of the lower extremities.

Laboratory studies gave negative results except for the urinalysis, which showed a trace of albumin and innumerable white cells. The complement fixation and the flocculation test of the blood for syphilis were negative. The spinal fluid was clear, and the pressure varied from 7 to 14 mm. of mercury. The fluid contained 4 cells per cubic centimeter and 45 mg. of protein and 60 mg. of sugar per hundred cubic centimeters. The colloidal gold curve was normal.

During her hospitalization she showed a progressive involvement of the upper extremities. Within seven weeks the sensory loss had extended to the level of the fourth cervical segment. Costal breathing was now absent, and diaphragmatic breathing was labored. Marked dyspnea developed, and the patient became slightly cyanotic. She expectorated moderate amounts of sputum and complained of difficulty in swallowing. Involuntary defecation of which she was unaware developed. All attempts at establishing an automaticity of the bladder were unsuccessful; so continuous drainage by catheter was instituted. Breathing became more and more difficult and the pulse imperceptible, and the patient died two months after admission.

During her entire hospital stay, her temperature remained normal except for a moderate elevation, to 100 F., for a few days. Terminally there was leukopenia, with 2,400 leukocytes and a normal differential count.

This patient presented a typical picture of so-called Devic's syndrome. The occurrence of ascending myelitis and concomitant bilateral loss of vision not associated with a febrile or toxic state makes the syndrome complete. The ascent of the process into the cervical portion of the cord, with respiratory difficulty, is a little unusual, since terminal respiratory and cardiac failure are uncommon in the literature. Van Bogaert [8] published a case that was at first considered to be an

8. van Bogaert, L.: Erreur de diagnostic; neuromyélite optique aiguë, premier stade d'une sclérose en plaques typique, J. de neurol. et de psychiat. **32**:234, 1932.

instance of Devic's disease, but since ataxia, intention tremor and scanning speech later developed, the author was forced to change his diagnosis to multiple sclerosis. Such a sequence of events did not occur in our case. Acute disseminated encephalomyelitis following an exanthem or vaccination against smallpox or rabies occasionally produces bilateral visual loss and myelitis. The patient, however, usually reveals symptoms of diffuse cerebral, brain stem and cerebellar involvement. Such symptoms were not present in our case. Schilder's encephalitis periaxialis diffusa, as well as other types of diffuse cerebral sclerosis, is often included in discussions of the differential clinical diagnosis in articles on Devic's disease. Marinesco and others [9] and Guillain and his co-workers [10] reported cases that they believed represented both Devic's disease and diffuse cerebral sclerosis. The state of confusion regarding these demyelinating conditions was well brought out by Baker and Gerber.[11] However, the present case presented no symptoms suggestive of a diffuse cerebral involvement.

Autopsy.—Most of the changes were limited to the nervous system, although bronchopneumonia, pulmonary edema and chronic passive congestion of the liver were observed. Both optic nerves were so small and thin that their appearance revealed unmistakable atrophy. The gross examination of the cerebrum, brain stem and cerebellum gave essentially negative results. Some segment of the cord appeared to be smaller than normal, and a curious type of gelatinous-like softening was visible in its center.

Sections from various regions of the nervous system were removed and prepared with the following stains: hematoxylin and eosin, Perdrau's stain, Mallory's phosphotungstic acid hematoxylin, Holzer's stain, Heidenhain's modification of Mallory's preparation, Bodian's stain and Weigert's stain.

The histologic changes were limited almost exclusively to the spinal cord and the optic nerves. With the Weigert stain the cord revealed an extensive demyelinization throughout. At the sacral level the destruction of myelin was complete, and at the thoracic level it was limited to the dorsal and the lateral columns (fig. 1), while in the cervical segments it involved only the anterior columns. The destruction of tissue showed a pronounced tendency to be centrally located, although in a few segments where the involvement was more extensive it did extend to the surface of the cord. The demyelinated areas were never sharply demarcated but showed a tendency to fuse gradually into the more peripheral, apparently intact tissues. Even the white matter that was grossly uninvolved displayed degenerative myelin alterations, such as swelling and neurokeratin clumping.

9. Marinesco, G.; Draganesco, S.; Sager, O., and Grigoresco, D.: Sur une forme particulière anatomo-clinique d'ophtalmo-neuromyélite, Rev. neurol. **2**:193, 1930.

10. Guillain, G.; Alajouanine, F.; Bertrand, I., and Garcin, R.: Sur une forme anatomo-clinique spéciale de neuromyélite optique nécrotique aiguë avec crises toniques tétanoïdes: Contribution à l'étude des crises toniques sous-corticales, Ann. de méd. **24**:24, 1928.

11. Baker, A. B., and Gerber, L. S.: Cerebral Sclerosis, Am. J. Dis. Child. **59**:522 (March) 1940.

The actual areas of parenchymal necrosis were largely occupied by microgliacytes, rod cells and numerous large fat granule cells. Areas of cavitation filled with scavenger cells were present within the more severely necrotized areas

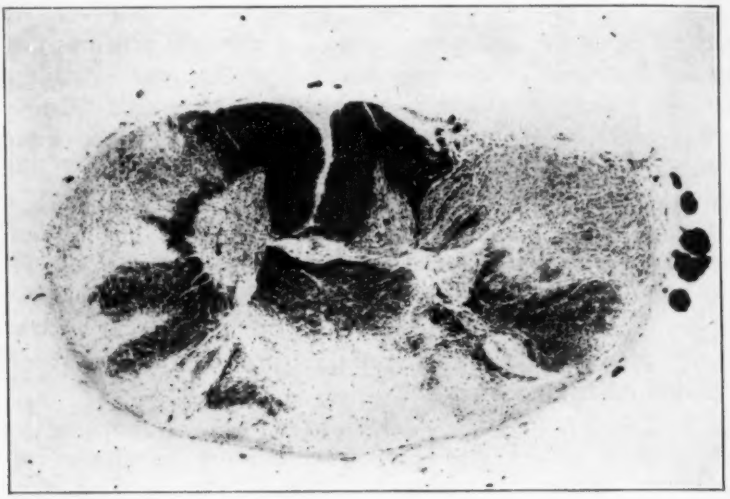

Fig. 1.—Sacral cord. There is an extensive but irregular destruction of the entire cord. Only the anterior columns and horns appear intact. (Weigert stain.)

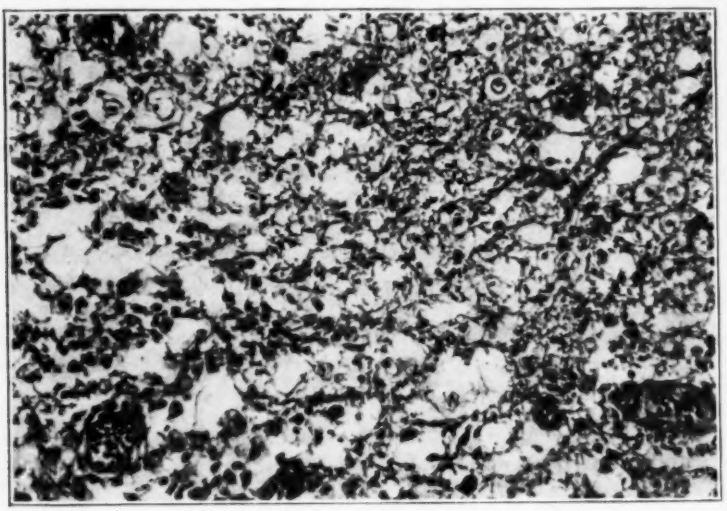

Fig. 2.—Section through the thoracic portion of the cord revealing extensive parenchymal necrosis. Note the vacuolization and the numerous fat granule cells. (Hematoxylin-eosin stain.)

(fig. 2). There also appeared to be an increased number of small blood vessels within or near the involved areas. Around some of these vessels there was a definite perivascular collar of mononuclear cells. Many vessels with no perivascular

exudate revealed fibrosis and hyaline degeneration, the walls being thickened and the lumens narrowed. An occasional petechial hemorrhage was seen.

There were marked axon swelling and disintegration in the areas of softening. Many fibers even in the apparently intact areas showed tinctorial loss and irregular swelling. In the axons of the nerve rootlets only minimal degenerative alterations were observed. The gray matter was also altered. In the cervical and the sacral regions the pathologic process was limited to the anterior horns, which were so completely destroyed that they could not be identified; while in the thoracic regions the cellular alterations were restricted predominantly to the posterior horns. The nerve cells of the cord generally displayed a great many toxic alterations. Nuclear changes, tigrolysis, cytoplasmic swelling, vacuolization, ghost cell formation, neurofibrillar disintegration and fragmentation were encountered. A few neurons appeared shrunken and pyknotic (fig. 3).

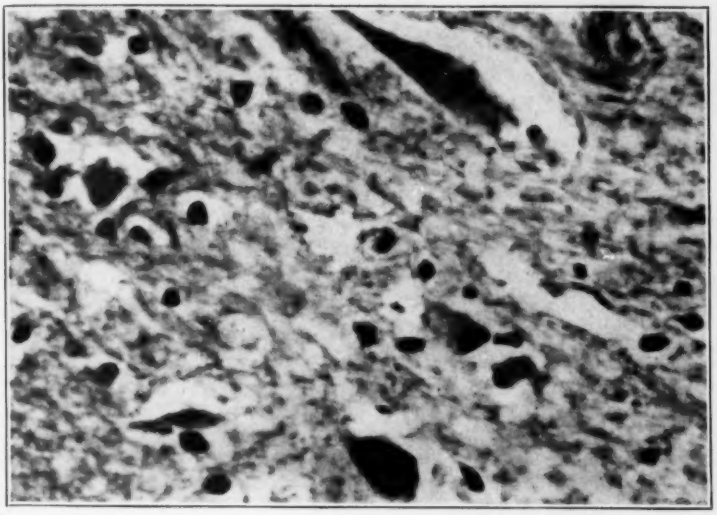

Fig. 3.—Section through the anterior horn of the spinal cord. There is a great paucity of nerve cells. Those present are shrunken and pyknotic. (Hematoxylin-eosin stain.)

Mild gliosis was present just under the pia and around some of the demyelinated areas. The macroglial cells consisted mostly of gemästete astrocytes which had formed few glial fibers. There were no areas suggestive of fibrous glial repair or a glial scar. Instead, the involved areas commonly revealed clasmatodendrosis or neuroglial degeneration. There was no significant connective tissue proliferation within the areas of injured cord tissue, although the Perdrau stain did reveal a minimal increase of reticulin in some areas.

The leptomeninges encircling much of the cord revealed moderate fibrosis, hyalinization and thickening. In many areas adhesions were found between the arachnoid and the pia. An occasional vessel within the meninges contained a perivascular collar of lymphocytes.

Generally, the changes in the optic nerves were profound and resembled in detail those already described for the spinal cord. Longitudinal sections of the optic nerves disclosed extensive destruction of all elements, with a few small cavity formations (fig. 4). Lymphocytes were seen in the adventitia of an occasional small vessel. In a few small areas there was a slight proliferaton of delicate reticulin fibers, but there was no significant increase of connective tissue elements.

The cerebral hemispheres, including the occipital lobes, were essentially uninvolved. The small cortical vessels revealed a slight endothelial swelling, but no definite proliferation. In the lower medulla there were observed a few small foci of demyelinization with an infiltration of various microglial elements.

The pathologic observations reveal a histologic picture similar to that already reported as Devic's disease. The thickening of the vessel walls

Fig. 4.—Optic nerve. There is a profound destruction of all elements, with complete eradication of the normal nerve architecture. Note the demyelinization, vacuolization and vascular changes. (Hematoxylin-eosin stain.)

in our case was not a frequent observation reported in the literature. However, since vascular occlusions or significant attenuations of lumens were not present, one cannot assume that the necrosis of the nervous parenchyma was due to primary vascular disease.

The similarity of this syndrome to multiple sclerosis has often been referred to in the literature. Usually in multiple sclerosis the lesions are more widely scattered throughout the nervous system and are of a focal nature. The plaques in multiple sclerosis may be recent or old and invariably when old reveal definite signs of glial repair. In our case, on the other hand, the involvement was of a diffuse nature and showed no plaque formation. Moreover, even with special stains there was observed

no increase of neuroglial fibers. We feel that the lack of glial repair, the absence of plaque formation and the absence of changes in the brain stem, cerebellum and cerebrum make a diagnosis of acute multiple sclerosis unlikely. Acute disseminated encephalomyelitis is ruled out by the absence of widespread perivascular demyelinization.

SUMMARY AND CONCLUSION

1. A clinicopathologic study of a case of Devic's disease is presented.

2. The limitation of the involvement to the optic nerves and the spinal cord plus the diffuse nature of the lesions with an absence of glial repair seems to us to favor the conception that acute neuromyelitis optica may be a disease entity rather than an acute form of disseminated sclerosis or encephalomyelitis.

SURVEY OF RECORDS OF GLAUCOMA IN OPHTHALMIC CLINICS

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By way of introduction it is necessary to state that recently the National Society for the Prevention of Blindness invited a number of New York ophthalmologists to constitute a glaucoma committee to undertake a campaign for reducing the percentage of blindness due to glaucoma.

So far the essential points of this task are:

1. To survey glaucoma work in ophthalmic clinics.

2. To disseminate knowledge on glaucoma among patients, general practitioners, social workers, nurses and all agencies interested in the prevention of blindness.

3. To urge the authorities in medical schools to allot sufficient time for teaching students the subject of prevention of blindness due to accidents and especially glaucoma.

4. To establish a glaucoma bureau or exchange which, among other activities, will make a census of all the cases of glaucoma in the clinics of greater New York and coordinate the material in such a way as to reduce the percentage of blindness from glaucoma.

5. To urge the rank and file of ophthalmologists to find a reasonable and practical way of teaching the 17,000 optometrists of this country the means of suspecting the presence of glaucoma in some of their patients.

6. To induce authorities in control of ophthalmic institutions to introduce improvements in the methods of handling patients with glaucoma and their problems if they deem such improvements advisable.

The fact that present methods of treating patients with glaucoma do not give satisfactory results has been recognized for a long time. Until now most of the attempts to solve the problem have been limited to investigations along scientific lines. However, even though glaucoma is essentially a scientific problem, the actual handling of patients with

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glaucoma is a problem for applied science, which can be solved by a method not exclusively scientific. This method should begin with an investigation of the efficiency of the present system of handling patients. (E. g.: How successful are ophthalmologists in discovering glaucoma at its earliest stage? What percentage of patients are receiving early and effective treatment, and how can the percentage of good results be improved?)

In order to obtain the proposed information an investigation of every phase of glaucoma work in ophthalmic clinics would be necessary. Such a study would uncover the weaknesses of the present system of handling the patients, and as a result necessary changes for improving the service might be suggested.

The purpose of this paper is to present a "survey form" with instructions, which has been prepared by some members of the Committee on Glaucoma of the National Society for the Prevention of Blindness, and also to report on the results of surveys made of case records of glaucoma in four ophthalmic clinics.

There are two methods which may be considered when a survey of records is being planned:

1. Formulate a number of questions and try to obtain the answers from the data found in the clinical reports and records.

2. Collect the data found in the records and summarize any significant material.

Both methods were used in the surveys, and the second proved the more satisfactory.

The absence of periodic reports analyzing clinical intake by diagnostic groups and a filing system which made it impractical to locate the records of all persons having a diagnosis of glaucoma prevented the securing of answers to the following questions:

1. Is there a clue in existing records indicating how glaucoma might be prevented?

2. Is the incidence of glaucoma [1] on the increase?

3. What percentage of the patients went to an ophthalmic clinic or private ophthalmologist for a first examination of the eyes only after glaucoma had reached a late stage?

Certain questions, as follows, were not satisfactorily answered from a review of the records that were available for study:

1. What percentage of cases had remained under observation for a period of five or more years?

1. This paper is concerned only with the subject of primary glaucoma.

2. In what percentage of cases was the diagnosis of glaucoma made in the early stage?[2]

3. What percentage of patients had one eye totally or almost entirely blind before applying for an ophthalmologic examination?

4. In what percentage of cases did one or both parents have glaucoma, and are there any definite types of constitutional anomalies or deficiencies prevalent in families in which glaucoma is prevalent?

Answers to the following important questions related to selection of appropriate ophthalmologic treatment were not found:

1. In what percentage of cases does cataract develop after operation?

2. In what percentage of cases does optic nerve atrophy continue to progress in spite of a successful operation (tension having been reduced to normal)?

3. What is the evolution of defects in fields of vision once they have made their appearance? Which types become arrested, which have a rapid progress and which recede?

4. Are there cases of spontaneous recovery or arrest, in which further surgical or pharmacologic treatment is not needed?

5. What happens to the refractive anomaly of the eyes months and years after a successful surgical operation?

The clinical records of cases of glaucoma appear to be unsatisfactory both for research purposes and for helping toward the intelligent handling of the individual case. However, it is possible that the records do not give a true picture of the service rendered.

DATA OBTAINED FROM THE RECORDS OF GLAUCOMA OF CLINICS A, B, C AND D

Clinic A.—During a period of thirteen years (1924-1937) approximately 1,500 patients with glaucoma attended the clinic. Of this number, the case records of only 58 were sufficiently complete to warrant analysis. Few patients remained under supervision over a period of years, and for those who did very meager diagnostic and progress notes were available.

1. Of the 58 cases studied, 11 remained under observation four years, 40 remained under observation five to nine years and 7 remained under observation ten or more years. The date of symptomatic onset was not recorded in 12 cases. The date of the first visit for ophthalmic care was not mentioned in 33 cases. The history of symptoms due to

2. The early stage is that in which the disturbed functions of the retina, optic nerve and balancing mechanism of the ocular tension are barely involved and easily reversible to normal.

glaucoma was not mentioned in 26 cases. The history of familial glaucoma was not mentioned in 56 cases.

2. The visual acuity of the 58 patients was:

	First Visit No. of Eyes	Last Visit (4-10 or More Years Later) No. of Eyes
Blind	24	37
5/200-20/70	29	33
20/60-20/20	63	41

The visual acuity was not reported for five eyes at the last visit.

3. No tangent screen examinations had been made in 13 cases; in 28 cases the average was one per year, and in no case was the average number of visual field examinations more than two per year.

4. The records failed to mention anything about the appearance of optic disks in 11 cases, about the depth of the anterior chambers in 8 cases and about the interval between the use of drops and tonometric examination in 55 cases.

Clinic B.—The material which resulted from the survey of clinic B was not suitable for analysis because a large proportion of the patients had come only for the purpose of obtaining a certificate for financial relief as blind persons and hence were not suitable subjects for treatment. It is worth mentioning that of 9,424 patients with ocular disease at clinic B, 300 had glaucoma.

Clinic C.—At clinic C the number of records available for study was exceedingly small—only 33 records from a clinic that is serving patients with ocular disease to the extent of tens of thousands per year! So few case records were available because there was no method for selecting them from files other than the ability of the clinic personnel to recall by name persons with glaucoma who had been followed for five years or more.

1. Of the 33 cases studied, 32 remained under observation five to nine years, and 1 remained under observation eighteen years. The date of symptomatic onset was not recorded in 16 cases. The date of the first visit for ophthalmic care was not mentioned in 31 cases. The history of symptoms due to glaucoma was not mentioned in 10 cases. The history of familial glaucoma was not mentioned in 33 cases.

2. The visual acuity of the 33 patients was:

	First Visit No. of Eyes	Last Visit No. of Eyes
Blind	11	13
5/200-20/70	28	17
20/60-20/20	27	23

The visual acuity was not reported for 13 eyes at the last visit.

3. No tangent screen examinations had been made in 5 cases; in 9 cases the average was one examination per year, and in no case was the average number of visual field examinations more than two per year.

4. The records failed to mention anything about the appearance of the optic disks in 15 cases, about the depth of the anterior chambers in 28 cases and about the interval between the use of drops and tonometric examination in 33 cases.

GENERAL OBSERVATIONS ON CLINICS A, B AND C

The procedures and facilities used differed from clinic to clinic and from examiner to examiner. However, most of the following observations apply to each of the clinics:

1. The clinical facilities were not standardized, differing in the various examining rooms. The lack of standardization was partially

Incompleteness of Records

	Clinic A; 1,500 Cases of Glaucoma; 1924-1937 58 Records No. of Cases	Clinic C 33 Records No. of Cases
1. Date of symptomatic onset not recorded	12	16
2. Date of first visit for ophthalmic care not recorded	33	31
3. History of glaucoma symptoms not recorded	26	10
4. The question of familial glaucoma not recorded	56	33
5. Tanget screen studies not made	13	5
Tanget screen examination, one a year	28	9
6. Appearance of optic disk not recorded	11	15
7. Depth of anterior chamber not recorded	8	28
8. Tonometry; when last drops used not recorded	55	33

responsible for the inconsistency in the measurement items on the records.

2. The completeness and the type of information found in the records varied greatly with the different examiners. (Occasionally an attending ophthalmologist who was particularly interested in glaucoma had tried to have all patients with glaucoma referred to a special clinic. This attempt remained unsuccessful, as the other members of the staff hesitated to cooperate.)

3. Social service follow-up was inadequate. The social service department was understaffed; hence little time was available for necessary home visits or conferences with patients to impress on them the need of regularity in using the medication prescribed and in attending the clinic.

4. The record room was understaffed. Hence there was no time for research or analysis of material in the case files.

5. There was an enormous waste of time due to lack of efficient organization of the entire system of handling patients with glaucoma, to incompleteness of records and to destruction of old records.

DATA OBTAINED FROM THE RECORDS OF GLAUCOMA AT CLINIC D

The total number of active cases of all types of glaucoma up to September 1941 was 796. There were 296 new cases during 1940. Of 283 cases of primary glaucoma, the records of 101 were studied in this survey. These cases had been under observation from five to twenty-one years.

1. Tabulation Summarizing Completeness of Records.—The number of cases for which information was incomplete or not recorded was as follows:

Date of onset of symptoms of glaucoma	42
Date when ophthalmic care was first sought	67
Description of symptoms	38
General health history	6 not reported; 58 "negative" [3]
Objective findings:	
Media	10
Fundi	4
Angle of anterior chambers	28
Pupils and irises	20
Results of gonioscopic examination (in use only a short time)	7

2. Central Visual Acuity.—This was as follows:

	Better Eye		Poorer Eye	
	First Visit	Last Visit	First Visit	Last Visit
	Number of Cases		Number of Cases	
20/30 or better	54	39	16	14
20/40 to but not including 20/70	25	17	10	5
20/70 to but not including 20/200	14	18	15	9
Blind economic blindness; 20/200 or less	8	22	26	26
Perception of light or of hand movements only	..	5	23	14
No perception of light	..	..	11	33

3. Diagnoses Found in the Records.—These were (1) chronic simple glaucoma, (2) chronic glaucoma, (3) chronic noncongestive glaucoma, (4) glaucoma, (5) acute glaucoma, (6) simple glaucoma, (7) absolute glaucoma, (8) acute congestive glaucoma, (9) infantile glaucoma, (10) congestive glaucoma and (11) chronic congestive glaucoma.

4. Visits per Year.—The average number of visits per year during the first five years was as follows:

First Year	Second Year	Third Year	Fourth Year	Fifth Year
10.6	7.0	5.	4.8	4.7

3. "Negative" for 58 patients 40 years old or over seems an unusually low prevalence of diseased conditions.

5. Tonometric Examinations per Year.—The average number of times tonometric examination was done during the first five years was as follows:

First Year	Second Year	Third Year	Fourth Year	Fifth Year
10.2	6.8	5.	4.5	4.5

6. Visual Field Examinations per Year.—The average number of times the fields of vision were charted in the first five years was as follows:

First Year	Second Year	Third Year	Fourth Year	Fifth Year
1.4	0.9	0.7	0.7	0.6

7. Summary of Deficiencies Found in the One Hundred and One Average Records of Glaucoma.—A. A certain number of records were incomplete as to (1) the approximate date of the onset of symptoms of glaucoma[4]; (2) the date when the patient first sought ophthalmic care; (3) a description of the symptoms; (4) a general health history[5]; (5) the depth and freedom of angle of the anterior chambers; (6) the size, shape and reactions of the pupils; (7) the condition of the irises, and (8) a familial history of glaucoma.

B. The central vision decreased in too large a percentage of eyes during the period of observation (five to twenty-one years).

C. There was a lack of agreement among the members of the staff as to the terminology used for diagnosis.

D. The average number of visits per year decreased too rapidly and too appreciably toward the fifth year and thereafter.

E. Tonometric measurements and measurements of the visual acuity were not recorded in the form of graphs; this fact reduced considerably the possibility that one might judge at a glance the course of the tension and the visual acuity in glaucoma over a period of five or more years.

The time between the last instillation of a miotic (including the dose) and tonometric examination was not recorded. Therefore, it was not possible to judge whether either or both eyes responded favorably or otherwise to the use of certain miotics and whether the formula for the frequency, dose and type of medication had been approximately established.

F. 1. The average number of times the visual field defects were charted is too small. 2. Daylight instead of standardized artificial light was used as a means of illumination of the tangent screen. (Daylight cannot be standardized for all seasons of the year and all times of the day.)

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4. Some of these must have been of symptomless cases.

5. Only patients admitted to the hospital for study received a thorough physical examination.

G. There is no record of general examinations or special tests (since so little time was at the disposal of the examiner).

H. Social service notes about the amount of cooperation on the part of the patient were kept in only a few cases.

8. Good Points Revealed by the Records.—Because of the weaknesses enumerated one should not overlook a number of excellent points discerned by study of the records of clinic D and the various activities going on there: the attitude of the staff members in handling patients with glaucoma and their problems; the careful recording of the ophthalmoscopic appearance of the optic disks and of the operative procedures, their dates and the visual results; the allotment of gonioscopy and perimetry each to one ophthalmologist, and the supervision by the director of the clinic of glaucoma work. All these factors are a good augury for further progress.

9. Further Findings at Clinic D.—A. Most patients returned to the clinic regularly, and at practically every visit notations on progress were made.

B. The existence of an index of cases of glaucoma and a well organized record room greatly simplified the study, as it took only a short time to get records from files.

C. The social service worker personally conducts each patient around the clinic from one service to the other. She also arranges for transportation in Red Cross cars if the patient is unable to travel alone or lives in an inconvenient district.

D. A pink sheet is filled out by the social service worker for patients who are difficult to get to return to the clinic for appointments. Information about how long a time the social worker has known the patient, about the social and economic status of the family (i. e. type of living conditions, care at home and any assistance from social agencies) and about any type of action taken, such as referral to other agencies or arrangements for transportation, is noted on this sheet. This record is filed in the folder with the medical record.

E. An appointment book is kept by the social worker so that she can tell at a glance how many patients to expect each day. In order to keep track of whether appointments are kept or not, a 3 by 5 inch card is made out for each patient, with appointment dates listed for each year. As appointments are kept these dates are crossed off. If an appointment is not kept, a letter is sent and an "L" placed on the card next to the date.

F. An important feature at clinic D is the glaucoma class, "which meets every two weeks during the months of October to June." All patients with glaucoma are invited to attend and bring any members

of their families or friends. Lectures are given in simple language by staff members. Attendance at these lectures averages twenty persons. This is really a successful method of informing the patients about their condition.

GENERAL OBSERVATIONS

The fact that the clinic D, though not less crowded than other clinics, accomplishes more and better glaucoma work raises the question: Why should other ophthalmic clinics not do as well or even better?

It is hoped that other ophthalmologists will undertake similar surveys of glaucoma in ophthalmic clinics throughout the country, making them available for study and criticism.

IMPROVEMENT OF CLINICAL SERVICE TO PATIENTS WITH GLAUCOMA

The following measures are recommended:

1. A special glaucoma clinic should be organized, with an experienced ophthalmologist in full charge, wherever the number of patients with glaucoma warrants it.

2. The unit comprising clerical, ophthalmologic, technical, nursing, social service, consultant and laboratory components should be under the supervision of the director.[6]

3. A printed "record form" should be adopted, containing the essential items for history taking, diagnosis and treatment, as well as other data necessary for future statistical and scientific research.

4. An efficient system of registering the patients, filing the records and cross indexing important items should be inaugurated.

5. Opportunity should be given to the members of the attending staff, especially to the younger ones, to acquire in a relatively short time the necessary knowledge of glaucoma work, its practical and scientific problems, and especially the technic of recognizing glaucoma in its earliest stage.

6. A survey of all phases of glaucoma work in the institution should be made annually and the results compared with those of previous years.

In ophthalmic clinics where the number of patients with glaucoma is small, the introduction of some of the measures enumerated will be of considerable help in reducing the high rate of blindness from glaucoma.

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6. For information concerning organization and equipment of clinics see also Berens, C.: Standards for Outpatient Service in Ophthalmology: I. Standards for Outpatient Ophthalmic Departments, Am. J. Ophth. **22**:870-875 (Aug.) 1939. Berens, C.; Williams, R. C., and Merrill, E. B.: II. Standards for Nursing Service; III. Standards for Medical Social Service, ibid. **23**:1352-1357 (Dec.) 1940.

Finally, an effort should be made to reduce the crowding of ophthalmic clinics (*a*) by preventing the wandering of patients from one clinic to another, (*b*) by educational efforts of social workers, (*c*) by stricter attention to efficiency and (*d*) by an increase in the number of members of the attending staff.

APPENDIX: SURVEY FORM FOR EVALUATION OF GLAUCOMA RECORDS

The accompanying survey form was prepared by the Committee on Glaucoma of the National Society for the Prevention of Blindness. Sections A, B and C should be printed on separate pages. Each finding should be entered in the corresponding column wherever it may be found on one of the three pages of the form. In this manner about fifteen records can be entered on each survey form. One would need only six or seven sets for a survey of one hundred records.

Explantory Notes for Glaucoma Survey Form Which May Be Useful to the Social Worker or Statistician Collecting the Data.—The numbers refer to columns on the form.

1. Date of First Clinic Visit: Enter date patient first came to this clinic.

2. Time Under Observation: Enter number of years patient has attended this clinic.

3. Date of Onset of Glaucoma Symptoms: Enter date patient first noticed any symptoms of glaucoma.

4. Date Patient First Sought Ophthalmic Care: Enter date patient first sought medical care for glaucoma symptoms. (This date is not necessarily of the first visit to this clinic.)

5. Description of Symptoms: Note diminution of vision, pain in eye, failing vision, halos and rainbows around lights and sensation of fog or film.

6. History of Familial Glaucoma: Note whether siblings, parents or other blood relatives have glaucoma.

7. General Health History: Note general examinations, examinations of nose and throat, dental and other examinations and laboratory findings.

8. Ophthalmic Diagnosis: Note type of glaucoma (i. e. acute, chronic simple, chronic congestive, etc.) and other ocular conditions not related to glaucoma.

9. Media: Note condition as follows:

Cornea: clear; deposits; clouded; steamy; edema; opacities; circumcorneal injections; vascularization of cornea.

Aqueous: clouded, turbid, clear; opacities.

Lens: clear; opacities (cataract).

Vitreous: clear; opacities; degeneration, etc.

10. Fundi: Note condition of disks as follows: normal; cupping; atrophic; excavation.

11. Angle of Anterior Chambers: Note condition as follows: normal, shallow, very shallow, obliterated; presence of pigment, particles of capsules, etc.

Survey Form for Evaluating Glaucoma Records

Clinic.....

A

Case Number	Date of First Clinic Visit (1)	Age, Sex and Race	Time Under Observation (2)	Number of Visits Each Year	Ophthalmic History: Date of Onset of Glaucoma Symptoms * (3)	Ophthalmic History: Date Patient First Sought Ophthalmic Care (4)	Ophthalmic History: Description of Symptoms * (5)	History of Familial Glaucoma (6)	General Health History (7)
1									
2									

B

Ophthalmic Diagnosis * (8)	Vision with Correction, First Visit: Right	Vision with Correction, First Visit: Left	Vision with Correction, Last Visit: Right	Vision with Correction, Last Visit: Left	Media * (9)	Fundus * (10)	Angle of Anterior Chamber * (11)	Pupil and Iris * (12)
1								
2								

C

Tension: First Visit: Right	Tension: First Visit: Left	Tension: Last Visit: Right	Tension: Last Visit: Left (13)	Average Times Taken per Month	Hours Since Drops	Fields: Perimeter	Fields: Bjerrum Screen (14)	Fields: Average Number per Year	Treatment *: Medical	Treatment *: Surgical (15)	Comment (16)
1											
2											

* Indicates right and left eyes separately.

12. Pupils and Irises: Note condition as follows:

Pupils: Reaction to light; size (approximate); dilated; miotic; immobile; oval; sluggish; rigid; inequality, etc.

Irises: Normal; atrophic; pigment scattered; congested; discolored; pushed forward; narrow; new blood vessels.

13. Tension: Enter measurement, noting method or instrument (i. e., fingers 1+, 2+, 3+; Schiøtz, or McLean) and time elapsed since last miotic.

14. Fields: Check whether patient had either perimeter or Bjerrum screen test or both.

15. Treatment: medical, enter names of drugs and how often used; surgical, enter names of operations and dates.

16. Comment: Enter any incidental notes of interest about patient, such as attendance at other clinics and hospitals.

1790 Broadway.

THE VOLLMER TUBERCULIN PATCH TEST

ITS POSSIBILITIES IN OPHTHALMIC PRACTICE

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The ophthalmologist would gratefully welcome a test for sensitivity to tuberculin simpler to prepare and to perform than the Mantoux test, provided reliance could be placed on its accuracy. The enthusiastic endorsement by numerous pediatricians of the tuberculin patch test described by Vollmer and Goldberger [1] prompted us to attempt an appraisal of this test in subjects suffering from ocular lesions. Our basis of comparison was a simultaneous Mantoux test on the opposite forearm, where 0.01 mg. of old tuberculin was injected intracutaneously. The latter procedure is the routine preliminary test for sensitivity to tuberculin as practiced at the New York Eye and Ear Infirmary.

In its present form [2] the material for the Vollmer patch test consists of a strip of adhesive tape 2.5 by 7.5 cm. on which are secured three squares of filter paper 1 by 1 cm. The squares are placed 1 cm. apart. The center square is saturated with glycerin broth and is stamped with the letter C to indicate its function as the control. The outer squares are saturated with undiluted tuberculin prepared after the method of Seibert.[3] Two such squares are employed in order to improve the efficiency of the test. The area generally selected for testing is the flexor surface of the forearm. The skin is scrupulously cleansed and defatted with acetone. This is important, as the presence of fat inhibits the action of tuberculin on the underlying skin. The adhesive tape is kept dry and is removed at the end of forty-eight hours, but the reading of the

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Lederle Laboratories, Inc., supplied the materials for the tests.

From the New York Eye and Ear Infirmary, service of Dr. Bernard Samuels.

1. Vollmer, H., and Goldberger, E.: New Tuberculin Patch Test, Am. J. Dis. Child. **54**:1019 (Nov.) 1937.

2. Vollmer, H., and Goldberger, E. W.: Comparative Study of Tuberculin Patch Test and Mantoux Intracutaneous Test, Am. J. Dis. Child. **56**:584 (Sept.) 1938; Evaluation of Tuberculin Patch Test (Vollmer-Lederle), ibid. **57**:1272 (June) 1939.

3. Seibert, F. B.: Am. Rev. Tuberc. **30**:713, 1934.

reaction is delayed for an additional forty-eight hours, that is until ninety-six hours from the time the patch is applied. A positive reaction is denoted by erythema and vesicle formation.

The advantages of the Vollmer patch test are numerous:

1. It is painless, quick, inexpensive and simple.
2. No assistance is required.
3. No instruments are needed, and no equipment need be sterilized.
4. The material if kept dry is extremely stable.
5. There are no severe local reactions and no general reactions.
6. The area of reaction is sharply limited; there is no uncontrollable spread of tuberculin to the adjacent skin.

In our series, all the tests were performed and the results read by the same observer (F. C. K. Jr.) in order to insure uniformity of technic and interpretation.

Before tabulating our results it will be worth while to summarize the conclusions of the numerous investigators in fields outside ophthalmology whose reports have been published. Their assessments of the patch test were made against Mantoux tests with old tuberculin or purified protein derivative. The latter is recommended by the National Tuberculosis Association for testing. Because of its stability and accuracy of standardization it is most likely to yield the greatest number of reactors. It is used in two dilutions: first strength, 0.00002 mg. of purified protein derivative, corresponds clinically to 0.1 mg. of old tuberculin, and second strength, 0.005 mg. of purified protein derivative (two hundred and fifty times the first dose), corresponds clinically to 1 mg. of old tuberculin. Most of the reports, however, are based on comparisons with old tuberculin rather than with purified protein derivative.

Vollmer in a large series of cases showed almost complete uniformity between the Mantox and the patch test.[4] In surveying the works of others he found ten different investigators reporting on 4,285 subjects; of these, 1,114 were positive reactors to the patch test and 1,119 were positive reactors to the Mantoux test.[5]

James G. Hughes[6] rated the efficiency of the tuberculin tests as follows: test with first strength purified protein derivative, 78 per cent; Vollmer patch test, 89 per cent, and test with second strength purified protein derivative, 100 per cent.

4. Vollmer, H.: J. Pediat. **16**:627, 1940.

5. (*a*) Taylor, G.: Am. Rev. Tuberc. **40**:236, 1939. (*b*) Steward, W. D.: J. Pediat. **13**:510, 1938. (*c*) Court, S. D. M.: Brit. M. J. **1**:824, 1939. (*d*) Weiner, S. B., and Neustadt, A.: J. Pediat. **14**:752, 1939. (*e*) Kerr, R. B., and Winograd, A. L.: New England J. Med. **222**:53, 1940. (*f*) Leonidoff, A. A.: Psychiatric Quart. **12**:754, 1938. (*g*) Hart, F. D.: Lancet **2**:609, 1938. (*h*) Saul: Personal communication to Vollmer. (*i*) Greenwald: Personal communication to Vollmer. (*j*) Shaw: Personal communication to Vollmer.

6. Hughes, J. G.: J. Pediat. **16**:171, 1940.

Other reports [7] have proved the patch test to be eminently reliable, with the exception of that by Peck and Wegman. These workers found the reaction to the patch test positive in only 30 per cent of the cases in which purified protein derivative I and II gave a positive reaction. Palin,[8] in a brief note, recorded the first ophthalmologic evaluation of the Vollmer test; he expressed the belief that it is equal to the Mantoux test.

AGE OF PATIENTS TESTED

All the tests mentioned except Palin's, for which no age groupings were mentioned, were made on young children and infants. In older patients the Vollmer patch test seems less reliable.

Logie [9] stated that the test has its maximum efficiency in children 6 years of age or less. Taylor [5a] found that in persons 50 years of age or more structural changes in the skin make the patch test less sensitive than the Mantoux. Kerr and Winograd [5e] tested children of high school age and found less accuracy than in the results recorded for young children. Rice [10] studied a group of college students and found that 23 per cent showed a negative reaction to the patch test but a positive reaction to purified protein derivative (strength ?).

TYPE OF TUBERCULIN USED FOR PATCH TESTS

The original test was done with New York Department of Health old tuberculin.[2] Later Vollmer turned to a tuberculin prepared from a synthetic medium,[3] which is two to four times as strong as the regular old tuberculin. It is not a purified product. Purified protein derivative in 1 per cent solution is not as effective, according to Vollmer and Goldberger.[11] Ouyang,[12] using a 2.5 per cent solution of purified protein derivative on filter paper, obtained 98 per cent agreement between the patch test and the test with first strength purified protein derivative.

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7. (*a*) Wolff, E., and Hurwitz, S.: Further Tests with Tuberculin Ointment Patch Test, J. A. M. A. **109**:2042 (Dec. 18) 1937. (*b*) Schick, B.: M. Clin. North America **23**:659, 1939. (*c*) Brown, M.: Canad. Pub. Health J. **30**:36, 1939. (*d*) Weddington, R. E., and Arnold, W. O.: J. Arkansas M. Soc. **37**:75, 1940. (*e*) Fineman, A. H., and Bair, G.: Evaluation of Tuberculin Patch Test, Am. J. Dis. Child. **60**:631 (Sept.) 1940. (*f*) Pearse, A. J.; Fried, R. I., and Glover, V. A.: Tuberculin Test and Mantoux Intradermal Test: Comparative Study of Seven Hundred School Children, J. A. M. A. **114**:227 (Jan. 20) 1940. (*g*) Kutscher, G. W., Jr.: South. Med. & Surg. **102**:135, 1940. (*h*) Craig, J. D., and Scheuer, L. A.: Arch. Pediat. **57**:177, 1940. (*i*) Bivings, L.: South. M. J. **33**:194, 1940. (*j*) Barber, D. J.: Rocky Mountain M. J. **37**:269, 1940.

8. Palin, A.: Brit. M. J. **1**:1006, 1939.

9. Logie, A. J.: Lancet **2**:917, 1938.

10. Rice, J.: J. Bact. **37**:233, 1939.

11. Vollmer, H., and Goldberger, E. W.: Old Tuberculin and Purified Protein Derivative in Tuberculin Patch Test: Comparative Study, Am. J. Dis. Child. **58**: 527 (Sept.) 1939.

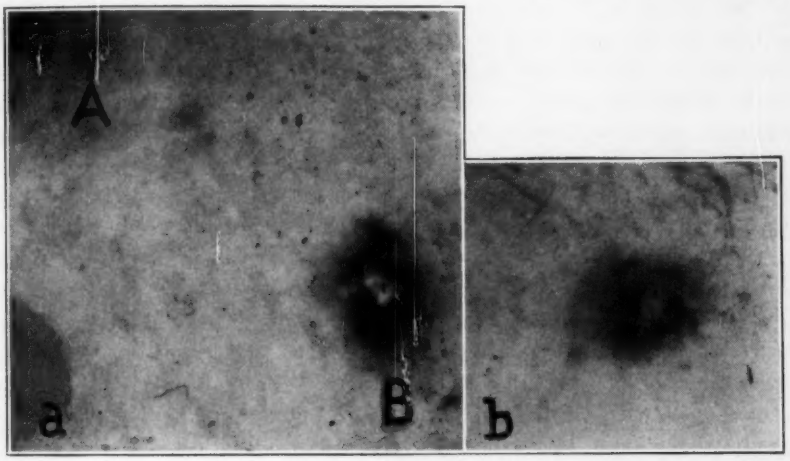
12. Ouyang, G.: Chinese M. J. **57**:51, 1940.

IRREGULAR REACTIONS

Delayed reactions are not infrequently noted.[13] In a few cases the acetone was found to cause an irritation which confused the reading of the reaction.[7i] In some cases local necrosis occurs.[7d] In other cases pruritus is marked. The erythema persists in others for a month or more, and a permanent brown stain may remain. Occasionally only one of the squares may react; at times one may react more strongly than the other.[8]

RESULTS OF THE PATCH TEST IN PATIENTS WITH OCULAR LESIONS

We tested 88 patients, taken at random from the various ophthalmic services at the New York Eye and Ear Infirmary, who presented logical



A positive reaction to the Vollmer patch test is shown in *a*. The reaction is much less definite at *A* than at *B*. A positive reaction to the Mantoux test (0.01 mg. of old tuberculin) in the same patient is shown in *b*.

reasons for having their sensitivity to tuberculin tested. These included patients with active and patients with inactive lesions. We thus selected a stratum of patients such as might be met in ordinary ophthalmic practice. The great majority of our patients were beyond 20 years of age; 27 of them were over 50. Our series included no infants or very young children; our youngest subjects were 11 years of age. Of the 88 patients tested, 71 were positive reactors and 17 negative reactors. The reaction to the Vollmer patch test was positive in 62 (87.3 per cent of the total reactors), and the reaction to the Mantoux test (0.01 mg. of old tuberculin) was positive in 70 (98.7 per cent of the total reactors).

13. Kerr and Winograd.[5e] Palin.[8] Rice.[10]

Of the 26 patients whose reaction to the Vollmer patch test was negative, 10 were picked up by the Mantoux test. One patient whose reaction was negative to the Mantoux test had a positive reaction to the Vollmer test.

For the most part the intensities of the reactions to the patch and the intracutaneous tests were parallel. In 5 cases the Vollmer test elicited a stronger response than the Mantoux; in 14 cases the reaction was more pronounced to the Mantoux than to the patch test. In 1 instance the reaction to the Mantoux test was 3 plus while that to the patch test was 1 plus; in all other cases in which an inequality existed the readings differed by only 1 plus.

COMMENT

Our series of 71 reactors permits a comparative rating of 98.7 per cent for the Mantoux test (0.01 mg. of old tuberculin), as against 87.3 per cent for the Vollmer patch test. As might be expected for a preponderately adult group, our rating of the Vollmer test was lower than that obtained in pediatric practice. Our rating is sufficiently high, however, to warrant advocating the Vollmer patch test as a preliminary step toward determining sensitivity to tuberculin. Our basis of comparison (0.01 mg. of old tuberculin) is weaker than the more generally accepted initial dose, 0.1 mg. of old tuberculin, and under this condition the Vollmer test would tend to draw a relatively higher rating. In the event of a negative reaction, a Mantoux test with 1 mg. of old tuberculin or with second strength purified protein derivative would be indicated. Positive reactions to the patch test provide the desired information accompanied with a minimum of the objectionable features which attend Mantoux testing. We found no necrotizing reactions in any of our patients and only a few delayed reactions. The exact value of this test in adults has still to be worked out in a large series of patients.

6 West Seventy-Seventh Street.

414 East Fifty-Second Street.

INTRANASAL DRAINAGE FOR CURE OF CHRONIC TEAR SAC INFECTION

NEW TECHNIC AIDED BY ELECTROCOAGULATION SO SIMPLIFIED AS TO BE AN OFFICE PROCEDURE

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Chronic tearing of the eye caused by obstruction in the tear conduction system may originate from either closed or misplaced puncta, from blocked canaliculi or from a blocked sac or nasolacrimal duct. The cause of the obstruction may be a scar due to injury, chronic inflammation of the mucous membranes leading to stenosis, a foreign body or pressure from a tumor. Tearing is increased by exposure to cold, wind, dust and fumes. Infection of the sac and its contents produces swelling and often a viscid, purulent fluid. This fluid, in passing through the puncta, causes chronic conjunctivitis, chiefly around the inner canthus; chronic swelling of the eyelids, which narrows the palpebral opening, and chronic swelling of the cheek.

Efforts to relieve such infection date back to antiquity. It was then believed that necrotic bone was the cause, and attempts were made to establish drainage from the lacrimal bone into the nose. Instruments were devised to perforate the skin and the lacrimal bone into the nasal cavity. Red hot perforators were plunged through the bone into the nose, the skin being incised first to avoid the ugly external scarring caused by a burn.

The first exact description of the anatomy of the lacrimal gland and the conduction apparatus was given in 1574 by Carcanus,[1] of Milan, a pupil of Fallopius. He also described the route taken by the tears. Antoine Maître-Jan [2] in 1707 again described the physiologic function of the apparatus, and J. T. Woolhouse was the first to take advantage of the knowledge. The physiology has been better comprehended only

Preliminary report read by invitation before the New York Society for Clinical Ophthalmology March 3, 1941.

1. Cumston, C. G.: History of Treatment of Surgical Affections of Lachrymal Apparatus, Ann. M. Hist. **3**:368 (Dec.) 1921.

2. Maître-Jan, A., cited by Guy, L.: Simple Dacryocystorhinostomy, Arch. Ophth. **20**:954 (Dec.) 1938.

recently, owing to the work of Whitnall, Schaeffer and others. Platner,[3] in 1724, following the advice of Woolhouse, his former teacher, extirpated the sac and bored through the lacrimal bone into the nose. Into the opening made he placed a gold tube.

Berlin [4] in 1868, because of dissatisfaction with other methods, removed the tear sac. The technic of his operation has been perfected and is the choice of many ophthalmologists today.

To reduce excessive tearing, which so often persists after removal of the tear sac, surgical measures, alcohol injections, roentgen treatments and electrocoagulation of the lacrimal gland have been recommended. Injection of alcohol into the sphenopalatine ganglion has been advised. Darkened lenses helped to reduce tearing caused by wind, cold, smoke, excessive light, etc. Toti, of Florence, in 1904 described his operation to reestablish the normal flow of tears into the nose by using an external approach similar to that of the original Platner method. Mosher [5] perfected and simplified Toti's operation. He advised previous removal, preferably with local anesthesia, of deviation of the nasal septum and of hypertrophy of the anterior tip of the middle turbinate, which narrow the nasal space, where adhesions may form and close the opening.

Dupuy-Dutemps and Bourguet [6] and others improved this method by the plastic suture of flaps made in the mucous membranes of the nose and sac to prevent closure (plastic dacryocystorhinostomy). Averbakh and Ivanova [7] reported on 1,200 operations done by this method in a ten year period at the Helmholtz Ophthalmic Hospital, Moscow, with a high percentage of cures (4.16 per cent failed). Possible intervening ethmoid cells and the too far forward placement of the anterior tip of the middle turbinate greatly increase the difficulty of such plastic suturing.

Killian [8] in 1889 reported a case in which he used the intranasal approach. After cutting off the anterior portion of the inferior turbinate, he inserted a Bowman probe as a guide into the nasolacrimal duct, which he opened after removing the bony wall covering it. Many

3. Platner, cited by Fleischer, B., in Elschnig, A.: Handbuch der Augenheilkunde, Berlin, Julius Springer, 1922, vol. 2, p. 1548.

4. Berlin, cited by Fleischer, B., in Elschnig, A.: Handbuch der Augenheilkunde, Berlin, Julius Springer, 1922, vol. 2, p. 1548.

5. Mosher, H. P.: The Mosher-Toti Operation on the Lachrymal Sac, Laryngoscope **31**:284, 1921; The Combined Intranasal External Operation on the Lacrimal Sac (Mosher-Toti), Ann. Otol., Rhin. & Laryng. **32**:1, 1923.

6. Dupuy-Dutemps and Bourguet: Note préliminaire sur un procédé de dacryocystorhinostomie, Ann. d'ocul. **157**:445, 1920; Procédé plastique de dacryocystorhinostomie et ses résultats, ibid. **158**:241, 1921.

7. Averbakh, M., and Ivanova (Mme.): Deux cents opérations de dacryocystorhinostomie plastique, Ann. d'ocul. **172**:913, 1935.

8. Killian, J.: Diskussion zu Seiferts Vortrag, 6. Versamml. suddeutsch. Laryngologen, 1889.

years later Yankauer used a similar technic. Caldwell [9] is credited with the first attempt, in 1893, to approach the tear sac intranasally. West [10] in 1910 perfected this approach. In certain cases of thickening of the sac wall or granulation, he advised intranasal extirpation of the sac. Many authors have reported modifications of this technic with a good percentage of success except in cases of fracture, a small sac, a sac with diverticula or a sac scarred by previous external operations. Bookwalter,[11] reflecting a large flap of the intranasal mucous membrane, opened a smooth round window through the lateral nasal wall and the lacrimal bone without the use of a guiding probe from above. He then tried to make a hole of the same size in the medial wall of the sac. The last, he stated, is the most difficult part of the operation. Walsh and Bothman [12] used Bookwalter's technic and reported 85.7 per cent of cures. They preferred this method to excision of the sac because there was no subsequent tearing and no external scar, as with Toti's method.

Khoronshitzky,[13] Hopman and others passed a probe through the canaliculus and the lacrimal bone into the nasal cavity as an aid in accurately locating the tear sac.

In tight noses or when there was fear of intranasal hemorrhage, von Eicken and later Kutvirt incised the fold of the upper lip and skeletonized and bit through the nasal process of the superior maxilla up to the sac, which was then extirpated (subcutaneous Toti operation). Veis [14] accomplished this more directly through an intranasal incision at the piriform aperture similar to the incision of Denker for operation on the antrum.

Lacrimal obstruction has been circumvented by transplanting the sac into the nose after cutting it free from the nasolacrimal duct.[15]

9. Caldwell, G. W.: Two New Operations for Obstruction of the Nasal Duct with Preservation of the Canaliculi, New York M. J. **57**:581, 1893; cited by Fleischer, B., in Elschnig, A.: Handbuch der Augenheilkunde, Berlin, Julius Springer, 1922, vol. 2, p. 1558.

10. West, J. M.: Die Technik der Eröffnung des Tränensackes von der Nase aus nach Erfahrung an 130 einschlägigen Operationen, Arch. f. Laryng. u. Rhin. **27**:504, 1913.

11. Bookwalter, C. F.: Intranasal Dacryocystostomy, Arch. Ophth. **49**:568, 1920.

12. Walsh, T. E., and Bothman, L.: Some Results of Intranasal Dacryocystorhinostomy, Am. J. Ophth. **20**:939 (Sept.) 1937.

13. Khoronshitzky, B.: Die perkanalikulare Tränensackdurchstechung als Einleitung zur intranasalen Tränensackeröffnung und als selbständige Operation, Arch. f. Laryng. u. Rhin. **28**:363, 1914.

14. Veis, J.: Eine neue Methode zur Operation der Tränensackes von der Nase aus, Arch. f. Laryng. u. Rhin. **34**:84, 1921.

15. MacMillan, J. A.: New Operation for Treatment of Lacrimal Obstruction, Am. J. Ophth. **4**:448 (June) 1921.

Wiener and Sauer [16] in 1920 and Sauer in 1923 and 1939 [17] reported a technic in which emphasis was placed on elevated flaps of nasal mucous membrane turned into the bony opening to discourage closure. This method is far less effective than the plastic suture of flaps in the external dacryocystorhinostomy of Dupuy-Dutemps and Bourguet. Granulations and new bone formation may close the opening in a percentage of cases (about 10 per cent) and must be combated repeatedly with a nasal punch, use of caustics, electrocautery or electrocoagulation.

Other efforts to overcome obstruction in the tear conduction system included the use of a solid or a hollow tube of metal and rubber, thread, catgut or horsehair inserted for long periods. A weak galvanic current was sent through thin wire inserted via the canaliculus and tear sac into the nasolacrimal duct by Terrien von Tripier,[18] Gorecki, Stephenson and Lagrange. The wire was partially insulated to protect the canaliculus and the tear sac. Recently the Hilgartners [19] cured a chronic catarrhal infection by using a galvanic current through a copper probe passed from above into the nasolacrimal duct.

Retrograde dilation of the nasolacrimal duct was practiced by La Forest,[20] Gensoul, von Hasner, Cossius, de Gourlay and others. Later Polyák [21] used this method but found it of no permanent value.

Galvanic and high frequency diathermic currents have been used, particularly by the French, in attempts to cure obstruction and infection of the tear sac. Medical diathermy has been applied externally [22] for dacryocystitis. Surgical diathermy has been employed after external incision to extirpate the lacrimal sac in cases of severe infection because it minimized extension of infection and threatening grave complications.[23] It was found valuable in obliterating the sac when

16. Wiener, M., and Sauer, W. E.: New Operation for Relief of Dacryocystitis Through the Nasal Route, J. A. M. A. **75**:868 (Sept. 25) 1920.

17. Sauer, W. E.: Intranasal Dacryocystotomy, Arch. Otolaryng. **30**:973 (Dec.) 1939.

18. von Tripier, T., and others, cited by Fleischer, B., in Elschnig, A.: Handbuch der Augenheilkunde, Berlin, Julius Springer, 1922, vol. 2, p. 1532.

19. Hilgartner, H. L., Jr., and Hilgartner, H. L.: Use of Copper Ionization in Treatment of Chronic Stenosis of the Lacrimal Duct, Am. J. Ophth. **18**:54 (Jan.) 1935.

20. LaForest, G., and others, cited by Fleischer, B., in Elschnig, A.: Handbuch der Augenheilkunde, Berlin, Julius Springer, 1922, vol. 2, p. 1532.

21. Polyák, L.: Die Sondierung des Ductus nasolacrimalis von der Nase aus, Arch. f. Laryng. u. Rhin. **12**:379, 1902.

22. Hunter, J.: Diathermy in Dacryocystitis, Canad. M. A. J. **22**:381 (March) 1930.

23. Hildreth, H. R.: Surgical-Diathermy Extirpation of the Lacrimal Sac, Am. J. Ophth. **19**:699 (Aug.) 1936.

necessary in the treatment of infantile dacryocystitis, in which hemorrhage and the limited field make surgical procedures difficult or impossible.[24] After external incision and opening of the sac, it has been used to coagulate the nasolacrimal duct, through which a rubber tube was passed for drainage into the inferior meatus and kept in place for twelve days.[25] Without an external incision, a medical diathermy current was sent through insulated sounds passed from above into the nasolacrimal canal.[26] Two or three treatments of about a half hour's duration were given, the current being regulated according to the sensation of the patient, who was not given any local anesthetic.[27] Weekers [28] in 1932 described a similar technic of diathermocoagulation used in reestablishing the permeability of lacrimal organs and stated that, although the early results were good, it was too soon to say whether they would be permanent. The fact that three years later he [29] published a modification of the surgical technic of Dupuy-Dutemps and Bourguet indicates that his results were not satisfactory.

Having succeeded by means of electrocoagulation in adequately, easily and permanently making an opening through bony atresia of the choana (which so often closes after surgical treatment), I [30] was prompted to apply electrocoagulation to the somewhat similar problem of obtaining a permanent opening through bone into the tear sac so that it might drain directly into the nose. Furthermore, by this means I could readily coagulate a tear sac entirely infected or one filled with granulations. Thus regeneration of the mucous membrane would be made possible without the difficulty of excision or curettage of the tear sac. A simple and accurate surgical technic aided by the use of electrocoagulation was developed and is here described. The surgical approach is so direct and the destruction of tissue so minimized that the entire procedure can be performed in the office, the patient being able to leave a short while after its completion.

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24. MacGillivray, A. M.: Infantile Dacryocystitis Treated by Surgical Diathermy, Brit. J. Ophth. **23**:630 (Sept.) 1939.

25. Spinelli, F.: Diathermische Rekanalisation des Tränennasenkanals, Klin. Monatsbl. f. Augenh. **91**:202 (Aug.) 1933.

26. Derfoug: La diathermie dans le traitement de l'oblitération des voies lacrymales, Bull. et mém. Soc. franç. d'opht. **44**:264, 1931.

27. Worms, G., and Filliozat: La diathermie des voies lacrymales, Bull. Soc. d'opht. de Paris, March 1931, p. 129.

28. Weekers, L.: Rétablissement de la perméabilité des voies lacrymales, Bull. Soc. belge d'opht. **65**:65, 1932.

29. Weekers, L.: Un procedé aisé et sur de dacryocystorhinostomie, Arch. d'opht. **52**:241 (April) 1935.

30. Morgenstern, D. J.: Congenital Atresia of the Postnasal Orifices: A Simple, Effective Office Technic for Treatment by Electro-Coagulation, Arch. Otolaryng. **31**:653 (April) 1940.

This report is based on 3 cases, in each of which a permanent cure was obtained. The treatment extended over six weeks, from the time of the operation until the discharge and sloughing had disappeared and mucous membrane lined the fistula and the tear sac. Should I find with further experience that the second coagulation treatment (given two weeks after the operation to insure permanency of the fistula) is unnecessary, the period of treatment can be reduced to four weeks. The first two cases were observed a little more than one year. The third case, in which there is a history of chronic tear sac infection of twelve years' duration, with mucocele and chronic swelling of the cheek, has been followed more than nine months. The mucocele was reduced, and, lastly, the chronic swelling of the cheek disappeared in about five months.

Recently I had the opportunity of operating on Mrs. G. A., 28 years of age, whose right eye had begun tearing three years before. Two months later the nasolacrimal duct had been probed, "with bleeding." There had been pus in the tear sac most of the time. The nose was exceptionally narrow, with a slight deviation of the septum to the right. Eleven years before the patient had undergone a plastic operation for the removal of a hump on the bridge of the nose. I found the lacrimal bone to be sclerotic, of ivory hardness, especially anteriorly and above and less so posteriorly and below, where the bone is more readily perforated. At the time of writing six months has elapsed since the operation, and the patency of the lacrimal fistula is maintained.

The operation in this case necessitated a modification of the procedure and is described under "Procedure."

The period of observation considered necessary to establish permanency of the opening varies from three months to over a year. One writer reported closure after a surgical opening had been maintained for one year. The reason for my employing electrocoagulation [30] is the fact that an opening made surgically through intranasal bone is much more likely to close than a similar opening made by electrocoagulation, especially if the surgical opening has not been maintained for about one year.

PROCEDURE

Chronic rhinitis and sinusitis, particularly ethmoiditis, should be controlled and nasal polyps removed. Roentgen examination may reveal a mucocele of the ethmoid sinus causing pressure on the tear conduction apparatus. A nasal septum markedly deviated above to the affected side may require correction, although this is infrequently necessary. With the subsidence of postoperative swelling, the operation on the tear sac can be performed. When the patient can undergo both operative procedures, the septal incision can be made on the

opposite side. At least one canaliculus must be patent. (If none is patent, efforts to attain patency should be made.) If the punctum is too small, it should be dilated.

One-fourth grain (0.15 Gm.) of morphine sulfate and 1/150 grain (0.0004 Gm.) of atropine sulfate in solution are injected hypodermically. Then the nose on the affected side is lightly packed with pledgets of cotton wrung out of local anesthetic solution. I prefer 2 per cent cocaine in physiologic solution of sodium chloride with one third of 1 per cent phenol and some added epinephrine. The nasal packing is removed after several minutes. This permits the nose to be more easily repacked tightly, particularly around the anterior tip of the middle turbinate.

A small amount of 10 per cent cocaine solution is applied to the punctum topically several times.

The nasal packing is removed from the inferior meatus, and the tear sac is thoroughly irrigated with boric acid solution. Most of the solution will return through the puncta, and some may pass into the nose.

About 0.5 cc. of 5 per cent cocaine solution is instilled into the tear sac.

The patient's electrode is placed in firm contact with the skin of the upper part of the back.

Several minutes later the sac is irrigated with physiologic solution of sodium chloride to remove the cocaine solution.

The remainder of the nasal packing is removed.

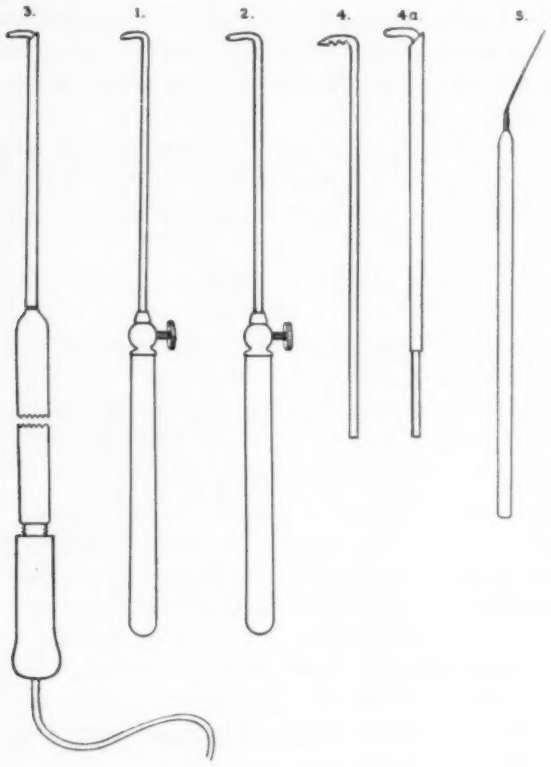
A dental root canal probe is passed into the punctum and through the canaliculus until the tip touches the medial wall of the sac. The handle of the probe is elevated in the frontal plane, and the operator feels downward along the medial wall of the sac until the bottom is reached. Here the point of the probe is gently forced through the lacrimal bone and any intervening anterior ethmoid cells into the nasal cavity at an angle of 45 degrees. A nurse supports the handle of the instrument in position while the operator inspects the inside of the nose to locate the tip of the probe.

The probe can usually be seen entering the nose just in front of the anterior tip of the middle turbinate. However, at times it cannot be seen even after it is pushed farther into the nose. This is due to enlargement of the anterior tip of the middle turbinate, which conceals the point of the probe. The probe can readily be touched (steel on steel) under the attachment of the middle turbinate by the operating hooked instruments described hereafter.

Four or five hooked instruments are fashioned from various sizes of stiff steel wire about 14 cm. long. The diameter of the wires varies from 0.057 cm. for gage 23 (Brown & Sharpe) to 0.825 cm. for gage 0.

The ends are sharpened bluntly and bent at a little more than 90 degrees. The bent ends vary from 0.5 cm. for the finest wire to about 1.3 cm. for the heaviest size. The heavier wires, having the longer bent ends, are made with dull points in order to avoid injury to the lateral wall of the tear sac. The finer sizes should be stiff enough to resist bending. The wires are slid into metal holders.

First the finest instrument is hooked from below onto the back of the guiding probe and rotated almost 90 degrees, so that its point is



Some of the instruments used.

directed toward the tear sac. In this position it is slid along the guiding probe, penetrating the lateral nasal wall up to the angle of its bend. This procedure is then repeated with increasingly larger-sized instruments. Palpating with the forefinger of the free hand applied at the inner canthus of the affected eye to the lateral wall of the tear sac, the operator feels for the movement of the dull point of the hooked instrument. If the bent part of the instrument is long enough, this point can easily be felt. Otherwise the next larger instrument is used, and

so on until the objective is attained. The guiding probe is removed. The dull point of the hook under the guidance of the palpating forefinger is readily rotated about in a vertical rectangle in the sagittal plane measuring slightly larger than the size of the tear sac (approximtely 4 mm. horizontally-anteroposteriorly by 12 mm. vertically[31]). This can be accomplished as follows: The dental root canal probe perforates the bottom of the sac in the frontal plane at an angle of 45 degrees. This probe automatically guides the largest hook into the bottom of the sac just anterior to the point of puncture, since the hook is bent at slightly more than 90 degrees. The palpating forefinger feels the dull point of this hook as it is now pulled forward firmly against the hard bone of the nasal process of the superior maxilla. The point of the hook is then felt just posterior to the lower end of the interior crest of the fossa sacci lacrimalis. This is the lower anterior angle of the vertical sagittal rectangle which is to be opened in the medial wall of the sac. By previously etching on the palpating forefinger a vertical rectangle 4 mm. by 12 mm. with any dye (for example, gentian violet), one can train the finger to sense the movement of the dull point of the large hook as it traces its periphery. From this point the periphery of the sagittal rectangle outlined on the finger is traced around upward, backward, downward and forward to the starting point.

Preliminary roentgen examination of the sac filled with radiopaque fluid, though not necessary, would permit more exactness in making the opening. The medial wall of the tear sac and simultaneously the opening through the lateral nasal wall leading to it are thus enlarged to their full extent. Special attention is directed to rounding the bottom of the tear sac. The palpating finger guides the instruments and thus prevents injury to the lateral wall of the tear sac, where, through the sinus of Maier and the valve of Rosenmüller (Huschke), the tears enter. The tear sac is copiously irrigated with physiologic solution of sodium chloride through the newly formed opening into the nose. There is scarcely any bleeding. Whatever little there is should be dried. Short pieces of sterile, dry, soft cotton cord are useful to dry the opening into the tear sac.

The largest hooked instrument employed is now insulated by being slipped into proper-sized thin rubber tubing up to and just around the angle of the hook, which is left bare. The hook is inserted into an electrode holder of a diathermy machine. The drying cord is removed and the insulated electrode quickly inserted into the tear sac. Its tip is palpated with the forefinger applied at the inner canthus. The end of the instrument being withdrawn medially into the nose about 2 mm.

31. Duke-Elder, W. S.: Text-Book of Ophthalmology, St. Louis, C. V. Mosby Company, 1932, vol. 1, p. 238.

to avoid the lateral wall of the sac, the diathermy current is turned on and off gingerly by a foot switch while the tip of the electrode is rotated two or three times, as before, in an area corresponding to the opening in the medial wall of the sac, a maneuver similar to that employed previously when the sac was being opened. In this way fragments of the torn medial wall of the sac are destroyed by means of electrocoagulation and the remainder of the sac lining is exposed to a lighter electrocoagulation. A current of 2,500 milliamperes when short circuited was used. This is equivalent to 250 to 300 milliamperes with the patient in the circuit. The slight degree of anesthesia of the sac enables the patient to direct the operator in determining the correct duration and amount of current.

Finally, the tear sac is irrigated with warm physiologic solution of sodium chloride. No packing need be used. The patient should be warned against blowing the nose and is advised to open the mouth widely if he sneezes. Because of the slightness of the trauma, the patient is soon able to leave the office with instructions to return in three days. Meanwhile he is to apply cool boric acid compresses over the eye and nose and to control the nasal swelling with a few drops of 1 per cent ephedrine in physiologic solution of sodium chloride applied every three or four hours.

A surprising amount of mucopus discharges into the nose from a mucocele.

When the patient is reexamined, the nasal cavity is shrunk and cleansed of drying mucopus discharging through the opening. The sac is again copiously irrigated with sterile warm physiologic solution of sodium chloride. This procedure is repeated in three or four days. The drying mucopus is kept softened, to prevent clogging of the opening, by a few drops of oil instilled twice daily into the nose.

The patient returns one week later, when the nose is shrunk and cleansed of drying mucopus from around the opening and the sac is irrigated with warm physiologic solution of sodium chloride. To insure against closure, the intranasal opening is packed with a sterile cotton cord soaked in the anesthetic solution originally used. After twenty minutes, 1 cc. of 5 per cent cocaine solution is instilled into the sac through the canaliculus. The intranasal packing is removed after fifteen minutes more and the area dried as before. The insulated electrode is again used and the sac and its opening into the nose lightly electrocoagulated. Finally, the sac is irrigated with warm physiologic solution of sodium chloride.

Each week for the next four weeks the sac is irrigated. The copious mucopurulent discharge lessens, and it completely disappears about six weeks after operation in the case of a tear sac infection of many years'

duration. When part of the anterior tip of the middle turbinate covers the opening, the first and second coagulations destroy just that portion. There are no granulations. Should crusting of the discharge be annoying, sterile cotton cord soaked in iodized oil is inserted each week through the opening into the sac and kept in for several days. Such a wick also aids in epithelization of the bony tract and in draining of infected matter from the sac, as it does in the case of chronic infection of the middle ear. The patient can easily remove the cord. Tearing soon disappears. The chronic swelling of the sac and of the area of the face beneath it slowly subsides. The palpebral aperture and the conjunctiva around the puncta approach the normal state. A permanent, clean, small fistula oval in shape, about 2.5 mm. by 3.5 mm., is the newly formed pathway for tear conduction.

A dacryocystorhinostomy usually leaves untouched the nasolacrimal duct, which may harbor residual infection. Such possible residual infection can be cared for by retrograde lavage or, if resistant, by subsequent electrocoagulation with an electrode bent at right angles and passed upward from under the inferior turbinate. Should the inferior turbinate be too closely placed against the lateral nasal wall, fracturing it toward the midline will facilitate the procedure. I believe that in cases in which only the nasolacrimal duct is stenosed and there is no concomitant infection in the tear sac, with production of viscid mucopurulent fluid, this method of retrograde lavage and retrograde electrocoagulation may bring permanent success sooner than the methods by which the nasolacrimal duct is approached from above. Much stronger surgical diathermy rather than the medical diathermy that must be employed in the approach from above can be used with safety in this bony region.

In the unusual case in which the lacrimal bone is sclerotic, perhaps of ivory hardness, as in a case of fracture, traumatic or operative, the procedure described must be modified (see case of Mrs. G. A., reported). The sclerosis is much more marked anteriorly and above, being less so posteriorly and below, where the bone is more readily perforated. The tissues surrounding the lacrimal bone are infiltrated with 1 per cent procaine hydrochloride solution. As an aid in obtaining anesthesia within the nasal cavity, in addition to cocaine topically applied an injection of procaine hydrochloride into the sphenopalatine ganglion is advisable. A stiff, pointed (not sharp) straight instrument heavier in caliber than the dental root canal probe otherwise used is employed. This is inserted through the previously dilated punctum and canaliculus. A sharp hammer tap on it punctures the less sclerotic area (posteriorly and below). Several such perforations are made, advancing anteriorly and above to the harder bone. To enlarge the small perforations made through the sclerotic lacrimal bone, the largest hooked instrument is

modified. Its dull point is sharpened, and to aid further in the removal of the sclerotic bone, the inner side of two such large hooks are filed down to a sharp edge, one in a plane parallel with (*4* in the accompanying illustration) and the other at right angles to a plane passing through the instrument. A jeweler's file is used on this edge to form three or four sharp saw teeth. Once the lacrimal bone has a small opening made through it and the sharpened tip of the modified large hook is palpated with the forefinger applied at the inner canthus, the hook is removed. A similar modified hook having a dull point is substituted to complete the removal of the sclerotic lacrimal bone without injuring the soft tissues. The bony opening having been properly enlarged, electrocoagulation follows, as in the ordinary case.

In cases of fracture in which the sclerosis is marked, before the formation of pus has taken place it would be interesting to employ retrograde electrocoagulation via the nasolacrimal duct, thus obviating the necessity of perforating the sclerotic lacrimal bone.

Two additional related uses for electrocoagulation (aided by indwelling threads) are (1) to reform closed canaliculi and (2) to reestablish the flow of tears into the nose in cases of excessive tearing following tear sac excision.

CONCLUSION

The technic described achieves with the least possible injury a permanent cure of chronic infection of the tear sac. Removal of the enlarged anterior tip of the middle turbinate, required in other methods, is not necessary. Preliminary submucous resection of the nasal septum is reduced to the lowest possible frequency. No incision or lifting of flaps and no chiseling or drilling with a burr is required. The most difficult part of all other intranasal technics is, as Bookwalter stated, "to enlarge the opening in the sac to the size of the bony opening." The effort to overcome this difficulty by pushing the sac into the bony opening with a heavy Bowman probe in order to visualize a part of it can at best be only partially successful. It is most difficult when the sac is small, tied down by scar tissue or filled with granulations; when a wide space intervenes between the medial wall of the sac and the nasal cavity, or when the medial wall of the sac is so softened by disease that the probe perforates it.

In contradistinction is my technic, by means of which the probe from above accurately guides the instruments into the sac and need not be removed until the final step. The palpating forefinger of the free hand applied to the inner canthus of the affected eye controls the intranasal instrument in enlarging the opening of the medial wall of the sac to its full extent. It does so easily without injury to surrounding tissues.

Unlike surgical excision, curettement or chemical destruction of the sac, indicated when the sac is filled with granulations or scar tissue or is badly diseased, electrocoagulation destroys the contents and the mucous membrane lining of the sac wall and, to a lesser extent, the sac itself. This leads to regeneration of the mucous membrane with the least possible tendency to granulation, so frequent in surgical procedure.

In cases of tuberculous or congenital syphilitic infection, in which, as Hopman stated, there is a marked tendency to new formation of bone, electrocoagulation is especially valuable. In cases of acute inflammation in which serious complications threaten, this technic starts instant drainage with the least possible surgical intervention and the almost simultaneous sealing of vascular channels that may reach vital structures. When indicated, complete removal of infection is accomplished by retrograde electrocoagulation of the nasolacrimal duct. Other dacryocystorhinostomy methods leave this duct untouched. The smallness of the final opening minimizes the danger that air or infected matter will be blown from the nose into the sac and through the canaliculi. Halle sought to attain this desideratum by covering the bony opening into the sac with the elevated flap of nasal mucous membrane. Through this he made a small perforation. He was not successful, owing to bony closure.

Because of the slightness of the surgical intervention and the subsequent coagulating action of the electric current, bleeding and possible infection both operatively and postoperatively are reduced to the lowest possible degree. This is indeed a comforting factor when the possibility of operative and postoperative hemorrhage following other methods is considered.

As far as I am aware from a review of the literature, the technic I have described is the first that employs hooks of simple construction, aided by electrocoagulation of the sac and the bony intranasal opening to it under accurate guidance by finger palpation, with the least possible injury and the attainment of a small permanent fistula. By retrograde diathermic catheterization of the nasolacrimal duct (which may be all that is required in cases of stenosis without infection), complete eradication of infection from the tear conduction system is achieved.

I wish to emphasize again that, in addition to many noteworthy advantages of this technic over other methods, because its surgical approach is so direct and destruction of tissue so minimized, it can be employed as an office procedure.

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THE EYE IN ADRENAL SYMPATHICOBLASTOMA (NEUROBLASTOMA)

IMPORTANCE OF OCULAR FINDINGS, WITH FIRST PATHOLOGIC REPORT OF METASTATIC TUMOR IN CHOROID

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Adrenal sympathicoblastoma, or neuroblastoma, as it is commonly called, is a malignant tumor occurring almost exclusively in infants and children. Burch found that it does rarely occur in adults. The typical cell is an embryonal nerve cell derived from neural ectoderm and is the primary sympathetic cell. Bailey and Cushing used the term sympathicoblasts, applying it to a group of undifferentiated pluripotential cells derived from the ganglion crest. These migrate into the visceral areas to form a primordium of the sympathetic nervous system and finally differentiate into more mature forms, namely the unipolar and the multipolar neuroblasts. This tumor has the same embryonic origin as the medulla of the suprarenal gland and the adjacent sympathetic ganglions and may arise from either. Bailey and Cushing expressed preference for the term sympathicoblastoma because not all cells in the tumor are potentially neuroblasts. Some may differentiate into chromaffin cells. Sympathicoblastoma is a malignant neoplasm originating from embryonal pluripotential cells of the sympathetic nervous system. In most of the cases reported the neoplasm grew from the adrenal medulla, but it may arise from embryonal sympathetic cells or sympathicoblasts anywhere in the body.

HISTOPATHOLOGY OF SYMPATHICOBLASTOMA

The histopathology has been described by Askin and Geschickter, by Lehman, by Geschickter and by Wright, who in 1910 was the first to show that this tumor is more properly called neuroblastoma because of the resemblance of the cells to cells of the sympathetic nervous system. He showed that the presence of fibrillae and rosettes is characteristic. The tumor consists of small cells which have hyperchromatic nuclei, are poly-

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morphous, contain little cytoplasm and lie in dense new-formed connective tissue. Delicate fibrils may arise from the cells. The cells are usually grouped, densely packed, and may be connected by a strand of protoplasmic processes. The grouping has the appearance of an embryonic ganglion of the sympathetic nervous system (Wahl). The cells may also be clumped as a rosette, arranged around a central mass of fibrils. Among these cells, larger round cells may be found, with larger pale vesicular nuclei and a larger rim of cytoplasm. These were called embryonic ganglion cells by Lewis and Geschickter.

Rosettes were found in only 30 to 50 per cent of the reported cases. Fibrils are often absent because the more embryonic and undifferentiated cells do not produce them. They are very unstable. Leinfelder stated that rosettes or fibrils should be present for a positive diagnosis. In their absence the typical cells only suggest neuroblastoma.

Since the characteristic findings are highly undifferentiated small round cells with a considerable amount of fibrillar material, the tumor is often confused with other highly undifferentiated neoplasms, as in the cases reported before Wright's paper appeared and in many cases in which the diagnosis was made from biopsy alone.

Bailey and Cushing suggested that the term rosette be used only for a small canal surrounded by primitive nerve cells. The ball-like aggregations, more typically mosaic, are characteristic of pseudorosettes. Kato and Wachter stated the belief that they indicate cytologic immaturity. True rosettes show relative maturity.

Verhoeff wrote that rosettes of metastatic sympathicoblastoma are entirely different from rosettes of retinoblastoma. He found typical rosettes in 2 of 17 tumors of the latter type. The rosettes represent an attempt to form sympathetic ganglions. There is no membrane at all, and the space is filled with fine embryonic nerve fibrils. The rosettes of retinoblastoma have a membrane around the lumen through which embryonic rods and cones project. In true glioma of the optic nerve rosette-like structures are seen with cells arranged around blood vessels. These may be called pseudorosettes.

REPORT OF CASES

Four cases of adrenal sympathicoblastoma observed in 1936 and 1937 in consultation with members of the department of pediatrics, in all of which there was striking similarity in the ocular complications, prompted this report. These cases illustrate the value of ocular signs for the diagnosis of adrenal sympathicoblastoma.[1]

1. During this period Dr. Paul R. Cannon informed me that the department of pathology did autopsies in 2 other cases. One tumor was a combined Pepper and Hutchison type in a girl 3½ years old and the other a tumor in a boy 24 hours old. Neither patient was seen clinically.

Case 1.—H. B., a 2½ year old white boy, was seen in May 1936 because of a hordeolum of the left upper lid. On November 16 the mother stated that a bluish discoloration had appeared on the left upper lid two weeks before and another on the right upper lid two days before. There had been no trauma. The family, birth, medical and developmental history were noncontributory. The bluish discoloration appeared gradually and became progressively worse. The patient was admitted to the hospital on November 19.

He was well developed and well nourished but had a pronounced waxy pallor. Although irritable, he was not acutely ill. The superficial veins of the forehead and the temporal regions were prominent. There was a bluish ecchymotic dis-

Fig. 1 (case 1).—The dilated blood vessels over the temple and the edema and ecchymosis of the lids.

coloration with moderate edema of the left upper lid (fig. 1). The left palpebral fissure was three-fourths the width of the right. There was a similar but less extensive ecchymosis of the right upper lid at the inner canthus. The fundi were normal. Moderately enlarged anterior cervical lymph nodes were palpable. There was a systolic murmur at the apex but no enlargement of the heart. The liver was palpable 2 cm. below the costal margin. No masses could be palpated in the abdomen. The temperature was normal. On the eleventh day a swelling appeared over the left temporal region.

On December 7 there were increased pallor, weakness and a poor appetite. A marble-sized mass appeared at the occipitoparietal junction on the left side.

The left temporal mass was the size of a baseball. The veins in the overlying skin were prominent. The ecchymotic areas of the lids were accentuated. There was moderate exophthalmos on the left with papilledema. The liver had enlarged to extend 5 cm. below the costal margin. No abdominal masses could be palpated.

Roentgen examination on admission showed a slight diastasis of the sutures of the skull and a granular pattern in the parietal regions. The second examination revealed more diastasis of the sutures and a slight increase of the digital marking, both of which indicated an increased intracranial pressure. Biopsy of the tumor of the left parietal region disclosed an unidentified type of rapidly growing sarcoma. Material from a sternal puncture and from puncture of a cervical lymph node and touch preparations from the biopsy specimen were studied and reported by Dr. Kato (Kato and Wachter). High voltage roentgen therapy was given, with

Fig. 2 (case 1).—Tumor cells in the choroidal blood vessels and the choriocapillaris.

no improvement. Severe anemia was present from the beginning. A blood count showed 960,000 erythrocytes, 8,000 leukocytes and 60,000 platelets; the hemoglobin content was 2.5 mg. per hundred cubic centimeters. The patient grew progressively worse and died Jan. 4, 1937.

Postmortem examination revealed a neuroblastoma of the right adrenal with metastases to the lumbar, periaortic, peribronchial and inguinal lymph nodes; metastases to the lungs, liver and skull, especially the petrosal portions of both temporal bones; tumor erosion and bony proliferation of the inner table of the skull and diastasis of the cranial sutures; subperiosteal hemorrhages of the ribs; fatty degeneration of the liver and kidneys; cloudy swelling of both kidneys; severe general anemia, and fatty infiltration and anemia of the myocardium.

The metastases to the skull were abundant, and there were gross hemorrhages beneath the scalp. The bony wall of the left orbit was soft, dark red, spongy and firmly adherent to orbital fat. There were hemorrhages into the superficial layers of fat. The mastoid cells were filled with mucus, blood and tumor tissue. Microscopic metastases existed in the left adrenal and in the spleen. There were

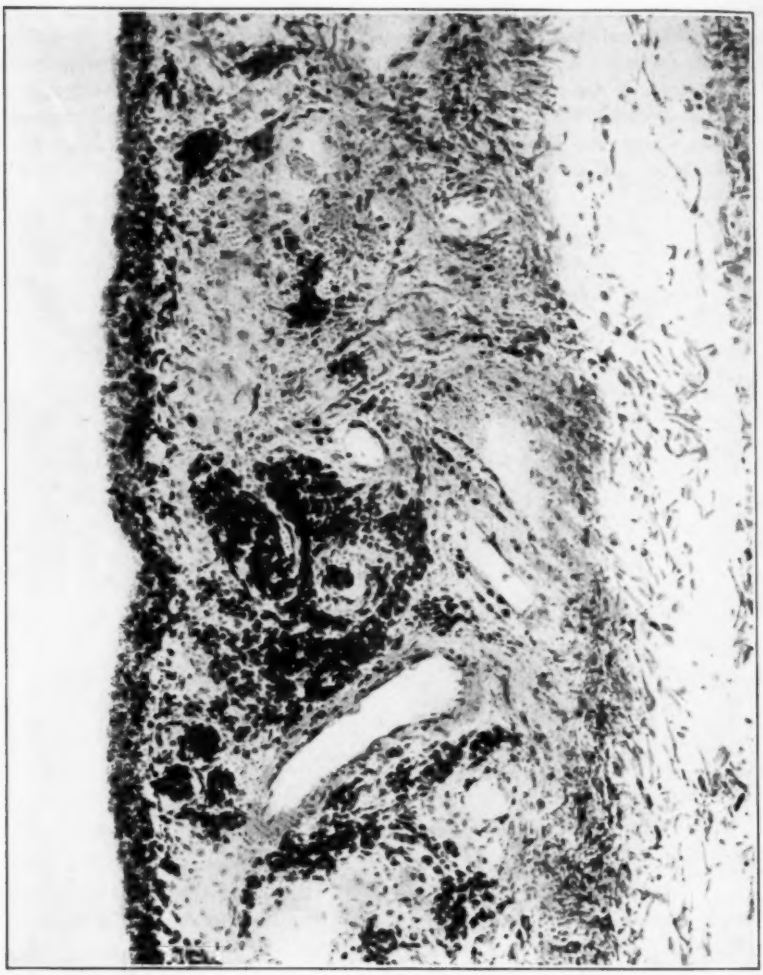

Fig. 3 (case 1).—Tumor cells in the blood vessels and extension outside the vessels of the choroid.

a few pseudorosettes in the large tumor of the right adrenal. At autopsy the posterior third of the left globe with a 16 mm. piece of optic nerve attached to it was removed and fixed in solution of formaldehyde.

Pathologic Examination of the Eye.—The specimen was embedded in celloidin (pyroxylin) and serially sectioned. Small bits of orbital tissue were attached to

the sclera and the optic nerve. Among the fat cells were a few small blood vessels which contained tumor cells. There were scanty nests of tumor cells outside of blood vessels. The sclera and its blood vessels were not involved. The intraocular portion of the optic nerve was swollen, but there were no hem-

Fig. 4 (case 1).—Tumor cells in the choroid (× 1,600).

orrhages. No blood vessels of the nerve contained tumor cells. The intervaginal spaces were distended. Along the pia and between it and the arachnoid and in the latter were a group of cells extending in linear fashion parallel to these sheaths. Perdrau's stain proved these to be nerve cells and not metastases from the tumor. The nerve itself was free from invasion. There was no invasion of the retina by tumor cells. In some sections there were microscopic hemorrhages in and on

the nerve fiber layers and in two sections very small hemorrhages and exudate between the retina and the choroid.

The choroid was invaded by typical tumor cells carried to it by the blood stream. In almost every section there were tumor cells in the choriocapillaris extending in linear fashion parallel and adjacent to the lamina vitrea. In many

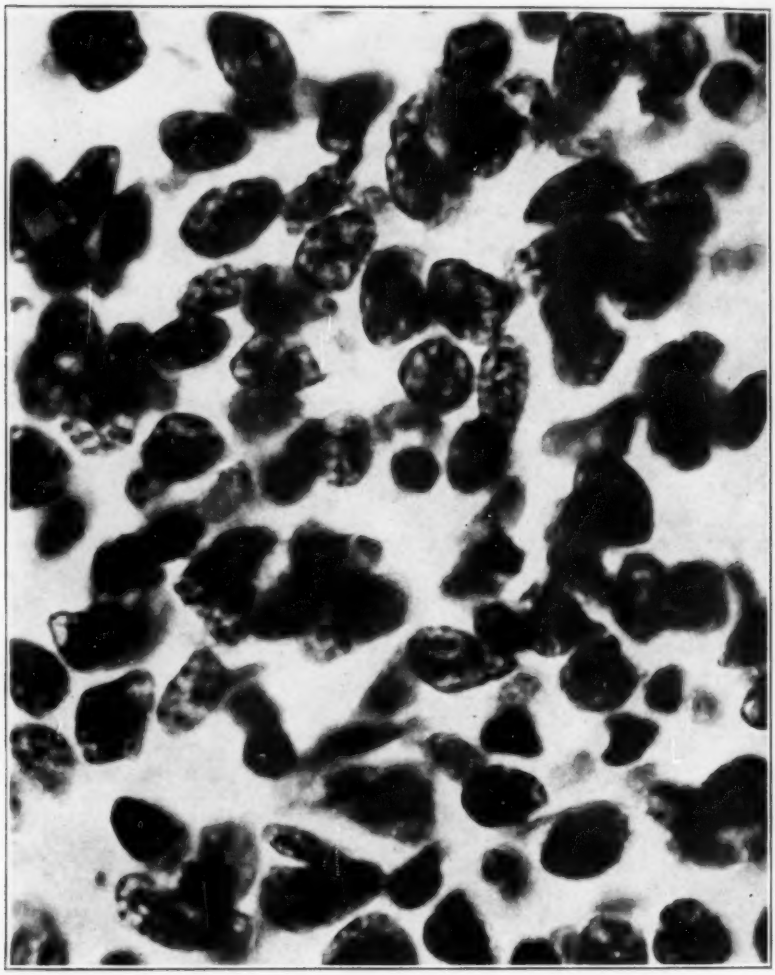

Fig. 5 (case 1).—Tumor cells of the right adrenal (× 1,600).

sections the medium-sized blood vessels of the structure contained tumor cells, some of their lumens being completely filled (fig. 2).

The largest invasion extended through one hundred and thirty sections cut at 18 millimicrons (fig. 3). Here some vessels were completely filled with tumor cells and the stroma between the blood vessels was invaded by dense masses of cells, some of which showed a pseudorosette formation. The stroma and the

suprachoroidea were apparently normal, and the pigment epithelium showed little change except over the site of the area of the largest invasion, where the cell walls were hazy and the layer appeared as a moth-eaten line of granular pigment.

Figure 4 shows a high power picture of the cells in the choroid. When this is compared with figure 5 it will be seen that the cells were of the same type as those of the adrenal.

The cell forms and arrangement conformed to the description given under the heading "Histopathology."

CASE 2.—D. R., a 3½ year old white boy, was admitted to the hospital on March 3, 1937 with a history of having had four months before an acute illness with a high temperature and pain in the right hip which migrated to other joints. There had been no swelling or redness around the joints. In December 1936 he had had a heart murmur which disappeared in a few weeks. In January 1937 all the symptoms recurred. He became weaker and had a rapid cardiac rate.

At physical examination the child appeared well developed and extremely pale. The veins of the forehead were dilated and very prominent. The frontotemporal sutures gaped out ¼ inch (0.6 cm.), and Macewen's sign was present. There was bilateral papilledema. The heart was moderately enlarged and had a systolic murmur at the apex and a rapid, regular rate. The liver could be palpated 3 fingerbreadths below the costal margin. There were no palpable masses in the abdomen. The circumference of the head was enlarged from 53 to 57 cm. Ecchymosis of the right upper lid appeared one month after admission. Numerous soft, fluctuant masses developed over the scalp. The papilledema increased, and paralysis of the external rectus muscles developed. The liver became large. A biopsy specimen from a bony protuberance on the distal end of the right femur proved to be round cell sarcoma. Roentgen examination revealed a marked diastasis of the cranial sutures and definite osteolytic lesions which were believed to be widespread severe leukemic infiltrations of the bones of the skull, humerus, femurs and pelvis. Later roentgenograms showed spicules in the subperiosteal masses at right angles to the shafts of both femurs at their distal ends.

The blood showed 1,260,000 erythrocytes and 3,300 leukocytes, with 15 per cent hemoglobin. The differential count was normal. Repeated blood transfusions, administration of Coley's toxin and high voltage roentgen therapy did not improve the patient's condition. He was discharged on May 13, 1937 and died at home. No postmortem examination was made.

The diagnosis was neuroblastoma of the adrenals.

CASE 3.—A. B., a 5 year old white girl, was admitted to the hospital on Nov. 15, 1937 for study because of fever which she had had on and off for eleven months, pain in the left knee and thigh which she had had for seven months and pain in the left side of the abdomen near the navel and in the lowermost left rib.

The patient had been in good health until an attack of "flu" in January 1937 with a slow convalescence followed by a low grade, constant fever for two months. The reaction to tuberculin was negative, and a roentgenogram of the chest revealed nothing significant. The pains disappeared in a few days.

The pain in the left side recurred in three and one-half months, and a tonsillectomy was done. Bilateral otitis media which occurred ten days after the tonsillectomy cleared up after sulfanilamide was used for one week. Pain recurred in the left knee and thigh, and a month later a mass was palpable over the psoas muscle. There was some improvement, with a gain in weight. For six months there were attacks of sharp pain in the left side lasting three days and recurring

every ten days. The pain was referred along the left leg. A rise of temperature to 103 F. followed, with nausea and emesis. One month before admission there was a severe attack of pain in the left side with rigidity of the abdomen, slight enlargement of the liver and anemia. There had been three or four attacks of epistaxis during the past six months and a loss of 12 pounds (5.4 Kg.) of body weight in one year.

At physical examination the child was pale, emaciated and not acutely ill but was sweating profusely. There was a large firm tender lobulated swelling at the base of the neck on the left side. A medium-sized node was found in the right anterior cervical chain. There was a soft systolic murmur over the apex and the aortic area. The cardiac rhythm was regular and the rate 108. The blood pressure was 102 systolic and 62 diastolic. The abdomen contained a large tender

Fig. 6 (case 3).—The ecchymosis and edema of the lids.

movable mass in the left hypochondrium. Many discrete movable nodules were palpable, and the lower thoracic and lumbar spaces were tender. Several 2 cm. firm movable nodules lay just anterior to the rectum about 5 to 6 cm. from the anal orifice. The temperature became normal, but the pulse rate was always between 120 and 140. The reaction to tuberculin (Mantoux test) was negative. The blood showed 3,200,000 erythrocytes and 9,300 leukocytes, with 52 per cent hemoglobin. The differential count was normal, as was the sedimentation rate. The urine was normal. Biopsy of the cervical nodes showed the characteristic cells and pseudorosette formation of metastatic neuroblastoma (sympathicoblastoma). Edema of the eyelids appeared on the tenth day and ecchymosis of the lids on the thirteenth day after admission. These gradually increased. There was no papilledema. The roentgen examination revealed a large mass lying behind the heart and extending to both sides of the spine and a partially calcified mass in the left psoas muscle. Roentgenograms of the skull showed nothing

abnormal. There was no involvement of the spinal column. Roentgen therapy and transfusion gave no relief, and the patient was discharged on the twenty-third day.

The final diagnosis was sympathicoblastoma of the adrenal region with metastases to the mediastinum and the lymph nodes. The patient died March 28, 1938. No autopsy was permitted.

CASE 4.—D. T., a 2 year old white boy, entered the hospital on Nov. 8, 1937. He had been well until three weeks before, when a swelling appeared over his left jaw. There was no fever. A few days later the abdomen and legs began to swell. Sulfanilamide was administered, after which the swelling of the abdomen and legs decreased but that of the jaw gradually increased. The reaction of the urine for albumin was 2 plus. For twenty-four hours before admission the urine had been scanty. The family history was noncontributory.

At physical examination the child was pale and undernourished; no abnormalities of the skull were observed. The fundi through dilated pupils were seen to be normal. The left side of the face and jaw was markedly swollen because of a firm warm mass over the left midposterior portion of the mandible. The mass was about 2½ inches (6 cm.) in diameter and protruded into the buccal cavity along the lower alveolar margin. The buccal surface was smooth. A carious molar was at the margin of the swelling. Examination of the chest gave negative results. The liver was palpable to 10 cm. below the costal margin. The enlarged left lobe was palpated 3 fingerbreadths below the costal margin. The spleen was enlarged. The extremities were normal. The temperature was normal. Examination of the urine gave negative results, and the blood showed slight secondary anemia which gradually became severe. The differential count indicated a mild shift to the left. The nonprotein nitrogen content of the blood was 45 mg. per hundred cubic centimeters. Roentgenograms of the left side of the mandible revealed an osteolytic process in the ramus, with fractures. Sternal puncture was of no aid in the diagnosis. Biopsy of the mandibular mass showed highly undifferentiated round cell sarcoma. Swelling of the right thigh developed, and roentgenograms showed a metastatic lesion in the lower half of the shaft of the femur, with new subperiosteal bone. Roentgen therapy to the mandible led to an increase of new bone. Six weeks after admission ecchymosis of the right upper lid appeared; this remained unchanged. Transfusion and roentgen therapy were of only temporary value, and the patient died Jan. 24, 1938. The final impression was of neuroblastoma of the adrenal with metastases to the left side of the mandible and the right orbit and femur.

The postmortem examination revealed neuroblastoma arising from the right adrenal gland, with massive metastases to the retroperitoneal lymph nodes, the periaortic chain, the pleural cavity, the sixth and eighth right ribs, the seventh and ninth left ribs, the skull (with involvement of the dura, especially the right parietal area), the orbital cavities (most pronounced on the right side), the left side of the mandible and the shaft of the right femur. There were superficial necrosis of the glans penis, severe compression of the inferior vena cava, marked edema of the right leg, ascites, bilateral hydrothorax, compression atelectasis of the lungs, early purulent bronchitis and bronchopneumonia, decided pallor of the muscles and anasarca.

Microscopic examination of the right adrenal gland revealed the presence of a neoplasm, the cells of which had large vesicular nuclei but little cytoplasm. Fibrils were not discernible. Numerous mitotic figures were present. Characteristic pseudorosettes were found throughout but were most numerous around blood

vessels. The tumor was extremely vascular but was undergoing necrosis. There was diffuse hemorrhage permeating all the tissue.

Case 1 was reported by Dr. Kato and Dr. Wachter, who discussed in detail the histopathologic examination at biopsy of the sternal marrow and a metastatic nodule from the skull. They only mentioned case 4 in a footnote.

COMMENT

These 4 cases of adrenal sympathicoblastoma conform to the clinical descriptions of Hutchison. The classification of the tumor into a Hutchison type and a Pepper type dates from the classic reports of these authors. The classification is only clinical, not pathologic. When the major metastases are local and involve only the lower and periaortic lymph nodes the tumor is known as the Pepper type. When the metastases are in the orbit, skull, meninges and long bones and the ocular signs occur early it is known as the Hutchison type. A third, or mixed, type does occur. In this there is some involvement of the liver and bone marrow but the skull is usually free from metastases.

In 1901 Pepper first described that type which now bears his name. It occurs at an early age, is often congenital (prenatal) and is highly malignant. The distended abdomen is due to a huge liver, which may be replaced by neoplasm. As a rule no jaundice or ascites occurs. Pepper has stated that adrenal "sarcoma" with bone metastases is found in the later years of childhood, but the diffuse hepatic growth is not present, although isolated neoplastic nodules may be present.

Hutchison, in 1907, was the first author to describe that type which now bears his name. Most of his ten cases were characterized clinically by some swelling of the bones of the skull. Unilateral or bilateral exophthalmos either preceded or followed. In two thirds of the cases ecchymosis of one or both eyelids occurred. In rare instances this was the first sign of the disease. A palpable abdominal tumor was found in one half of the cases.

In Kato and Wachter's review of 232 cases of adrenal neuroblastoma in children they found that the average age at which the tumor appeared was 2 years for the Pepper type and 4 to 5 years for the Hutchison type. Our patients were 2, 2½, 3½ and 5 years of age, an average of 3¼ years.

Their review also revealed that the sex incidence was almost equal for the Pepper type but that males were predominantly affected by the Hutchison type. The Hutchison type originated as often from the right as from the left adrenal, but the Pepper type originated most often from the right adrenal. This fact partially substantiates Frew's contention that when the neoplasm begins in the right adrenal the Pepper type will occur because of its intimate association with the liver, both directly by its

proximity and indirectly because of its vascular relationship. His contention that the Hutchison type occurs from the left adrenal because of its lymphatic connection with the periaortic and lumbar lymph nodes is not proved by these statistics.

This study proves that the clinical division is purely arbitrary and is based solely on the site of major metastases. Either type may produce metastases to both skull and liver in varying proportions. Askin and Geschickter discussed this overlapping of the Pepper and the Hutchison type. Our first and fourth cases clearly illustrate it.

Geschickter stated that the metastatic predilections for certain regions are dependent on neither cell type nor relation of the primary tumor to blood and lymph vessels but on the age of the patient.

The remainder of the clinical picture depends on intracranial pressure, hydrocephalus and evidence of diastasis of the bones of the skull. Localized areas of decreased density that occur in the skull and in the pelvic and long bones are due to the metastatic growth. Later in the disease characteristic new subperiosteal proliferations occur in the long bones, giving a peculiar roentgen picture of whiskers or fringes due to perpendicular lines formed by the bony spicules. Anemia, cachexia and weakness follow rapidly. The disease is rapidly progressive, and death occurs in a few months. The average duration of life after the appearance of the initial symptoms is about four and three tenths months (Kato and Wachter). Roentgen therapy is of only temporary aid.

The occurrence of ecchymosis of one or both lids alone or associated with exophthalmos not only should suggest adrenal sympathicoblastoma but may be diagnostic of the disease. Sturtevant and Kelly emphasized the fact that ecchymosis of the eyelids and proptosis in infants and children should arouse suspicion of an adrenal neoplasm. Seefelder stated that exophthalmos associated with ecchymosis of the lids in children makes it possible uniformly to diagnose the source of the orbital metastases.

Our first patient was seen initially in the ophthalmic clinic because of ecchymosis of the left upper lid. Postmortem examination proved the diagnosis and illustrated the overlapping of the two clinical types. Sternal punctures and biopsies of lymph nodes were of no aid to the correct diagnosis. In the second case the widespread bone metastases and the papilledema were the chief clinical findings. The biopsy showed only round cell sarcoma. The ecchymosis of the right eyelid suggested the presence of an adrenal tumor, and this suggestion was strengthened by the typical roentgen findings. In the third case a biopsy proved the diagnosis because of the presence of typical rosette formation in the specimen. Ecchymosis occurred one week after biopsy. In the fourth case the findings were atypical until suggestive roentgen appearances

were observed and ecchymosis of the right upper lid occurred. The diagnosis of adrenal sympathicoblastoma was confirmed at autopsy.

A review of the literature revealed 78 cases in which there were one or more ocular signs, such as ecchymosis, exophthalmos, papilledema and a tumor mass at the temporal side of the orbit. Exophthalmos occurred in 79.5 per cent of the cases, ecchymosis in 71.8 per cent, papilledema in 29.5 per cent and temporal tumor in 17.9 per cent. Only 2 patients with ocular symptoms had only papilledema or a temporal tumor mass. In 40 cases, or 51.2 per cent, ecchymosis and exophthalmos occurred together. The occurrence of ecchymosis alone or with exophthalmos can be diagnostic of adrenal sympathicoblastoma, because the other causes of ecchymosis of the lids, such as chloremia, leukemia, purpura, scurvy and trauma, can be excluded by the history or by laboratory examinations. Christian-Schüller disease would be difficult to differentiate if the characteristic exophthalmos were associated with ecchymosis. Such an association has not been recorded but might occur.

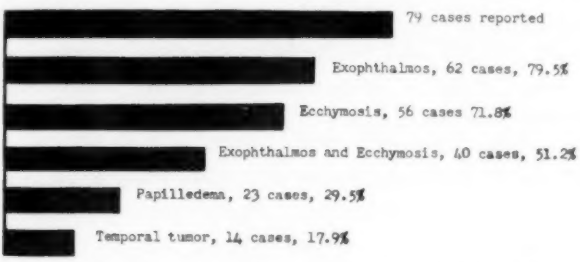
79 cases reported
Exophthalmos, 62 cases, 79.5%
Ecchymosis, 56 cases 71.8%
Exophthalmos and Ecchymosis, 40 cases, 51.2%
Papilledema, 23 cases, 29.5%
Temporal tumor, 14 cases, 17.9%

Fig. 7.—The incidence of various types of ocular involvement.

The type of ecchymosis is unusual. It usually begins 4 to 6 mm. below the eyebrow and gravitates to the lid margins. It is a deep purplish blue (fig. 6). In 1 of our cases the ecchymosis remained 4 to 6 mm. from the lid margin, and its lower border was irregular. The pathogenesis was discussed by Duke-Elder, who quoted Heerfordt's statement that effusions outside the muscle cone lying between the muscles and the periosteum can reach the conjunctiva and lids only as far as the orbital septum and that if a pressure of 40 to 50 mm. of mercury is exceeded they may percolate through the vascular apertures of the septum and infiltrate the superficial tissue of the lids.

If this is correct the metastases with hemorrhage must occur outside the orbital septum in the soft tissues, because ecchymosis may occur without any evidence of increased intraorbital pressure, such as exophthalmos. It is more likely that the metastases are in the orbital fat and that the hemorrhage percolates through the vascular apertures of the orbital system into the subcutaneous tissue of the lid without need for

increased pressure. The metastases to the orbit are probably hematogenous in the skull and dura and then by direct extension enter the orbit. They might even occur primarily to orbital fat.

SUMMARY AND CONCLUSIONS

Four cases of adrenal sympathicoblastoma with ocular manifestations are reported. Ecchymosis of the eyelids was the most constant finding, occurring in all 4 cases; papilledema occurred in 2, exophthalmos in 1, a temporal tumor in 1 and paralysis of the external rectus muscles in 1.

The importance of ecchymosis and exophthalmos as distinct aids to diagnosis is stressed, since biopsy often fails to provide the correct diagnosis.

The overlapping of the Pepper and the Hutchison type is well illustrated by the cases reported, all of which were of the Hutchison type.

This tumor metastasizes to the globe via the blood stream, as demonstrated by the presence of typical tumor cells in the medium-sized blood vessels of the choroid and the choriocapillaris in case 1.

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MECHANISM OF THE PRODUCTION OF EXOPHTHALMOS IN EXOPHTHALMIC GOITER

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The occurrence of exophthalmos in exophthalmic goiter has always been a most interesting and baffling pathologic problem to the medical profession, clinicians and experimenters alike. The importance of any condition as prevalent and as disfiguring as exophthalmos is apparent. It is hoped that a study of the mechanism of the production of ocular proptosis in the research laboratory may eventually lead to an understanding of the causation of both the exophthalmos and the other manifestations of exophthalmic goiter. At present there is no unanimity of opinion concerning the pathogenesis of the exophthalmos. Sufficient clinical and experimental evidence has been assembled to incriminate the sympathetic nervous system, the thyroid gland and the anterior lobe of the hypophysis. As the following review indicates, it is impossible to select a single local or general cause of exophthalmos at the present time.

ROLE OF ORBITAL DISEASE

Although the syndrome of exophthalmic goiter had been described previously by Parry [1] and Graves,[2] it was Carl von Basedow [3] who first paid particular attention to the exophthalmos and theorized as to its cause. Basedow suggested that the protrusion of the eyes was caused by hypertrophy of the posterior orbital structures, basing this assumption on the fact that the eye was normal in appearance and that he "could not push back the tense eyeball."

Observations recorded during decompression operations and at autopsies, as well as biopsy studies, serve to substantiate Basedow's

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1. Parry, C. H., cited by Major, R. H.: Classic Descriptions of Disease, ed. 2, Springfield, Ill., Charles C. Thomas, Publisher, 1939.

2. Graves, R. J.: Newly Observed Affection of the Thyroid Gland in Females, London M. & S. J. **7** (pt. 2):516-517, 1835.

3. von Basedow, C.: Exophthalmos durch Hypertrophie des Zellgewebes in der Augenhöhle, Wchnschr. f. d. ges. Heilk. **6**:197-204 (March 28) 1840.

hypothesis. Ashkenazy [4] observed macroscopic fatty degeneration at postmortem examination in all the orbital muscles, including the rectus muscles, of 4 patients with exophthalmic goiter. The first histologic description of the rectus muscles obtained at postmortem examination was recorded by Carl Fisher,[5] who noted parenchymatous degeneration of the muscle fibers and an excess of orbital fat as constant findings. R. Foster Moore [6] confirmed these results but also noted the presence of orbital edema, a finding later supported by Thomson.[7] Burch,[8] corroborating all these observations, described infiltration of the orbital fat by lymphocytes and wandering cells. Recently a report of the postmortem orbital examination in 15 cases of progressive post-thyroidectomy exophthalmos, the largest series ever reported, confirmed all these observations.[9]

Biopsy of the orbital tissues in 6 cases of exophthalmic goiter, in only 1 of which it was performed prior to thyroidectomy, revealed edema and infiltration of the fatty tissues.[10] Histologic study of the muscles showed enlargement in 2 cases and no change in 2 cases, and in the remaining 2 cases the sections did not permit an opinion. Naffziger [11] has performed decompression and enucleation operations on several patients with exophthalmic goiter afflicted with "malignant" exophthalmos. In each patient the muscle cone was tense and the individual muscles were fibrous. The orbital fat, however, appeared normal, and removal of the fat did not result in any improvement of the exophthalmos.

4. Ashkenazy, M.: Pathologisch-anatomische Beiträge zur Kenntnis des Morbus Basedowii, insbesondere über die dabei auftretende Muskelerkrankung, Deutsches Arch. f. klin. Med. **61**:118-186, 1898.

5. Fisher, C., in discussion on Parker, W. R.: Double Luxation of the Eyeballs in a Case of Exophthalmic Goiter, Tr. Am. Ophth. Soc. **19**:129-134, 1921.

6. Moore, R. F., in Trotter, W.; Fisher, J. H., and others: Discussion on the Diagnostic Significance of Proptosis, Tr. Ophth. Soc. U. Kingdom **43**:215-216, 1923.

7. Thomson, E. S.: Orbital Edema in Exophthalmic Goiter, Am. J. Ophth. **7**:27-35 (Jan.) 1924.

8. Burch, F. E.: Exophthalmos of Graves' Disease, Minnesota Med. **12**: 668-675 (Nov.) 1929.

9. Thomas, H. M., Jr., and Woods, A. C.: Progressive Exophthalmos Following Thyroidectomy, Bull. Johns Hopkins Hosp. **59**:99-113 (Aug.) 1936.

10. Smelser, G. K.: A Comparative Study of Experimental and Clinical Exophthalmos, Am. J. Ophth. **20**:1189-1203 (Dec.) 1937.

11. Naffziger, H. C.: Progressive Exophthalmos Following Thyroidectomy: Its Pathology and Treatment, Ann. Surg. **94**:582-586 (Oct.) 1931. Naffziger, H. C., and Jones, H. O., Jr.: The Surgical Treatment of Progressive Exophthalmos Following Thyroidectomy, J. A. M. A. **99**:638-642 (Aug. 20) 1932. Naffziger, H. C.: Pathologic Changes in the Orbit in Progressive Exophthalmos, with Special Reference to Alterations in Extra-Ocular Muscles and Optic Disks, Arch. Ophth. **9**:1-12 (Jan.) 1933.

Before accepting these observations one must remember that they were with a single exception made on patients with postoperative exophthalmos who had suffered from the proptosis for a long period. The possibility must therefore be admitted that the edema, hypertrophy of the fat and degeneration of the rectus muscles are secondary to the chronic exophthalmos. However, even if these pathologic changes are accepted as the mechanism whereby progressive exophthalmos is produced, one can hardly assume that they are responsible for the nonprogressive, rapidly reversible exophthalmos most frequently seen in exophthalmic goiter.

ROLE OF THE SYMPATHETIC NERVOUS SYSTEM

Claude Bernard [12] was the first to observe that stimulation of the cervical portion of the sympathetic trunk in experimental animals produces exophthalmos. This observation, in conjunction with the fact that tachycardia, hyperglycemia and an increase in the metabolic rate —all well known signs of exophthalmic goiter—can be evoked with epinephrine or by sympathetic stimulation, led to the concept that exophthalmic goiter results from overactivity of the sympathetic nervous system. Much evidence has accumulated in favor of this view.

Von Graefe,[13] in his original paper describing the clinical sign to which his name is now affixed, stated that lid lag is not the result of exophthalmos but, on the contrary, may be associated with almost any condition producing protrusion of the eyeball. It may appear and disappear during the course of the disease even though the exophthalmos persists. In 1 case, for instance, he observed that the lid lag disappeared after the administration of morphine. On the basis of these observations, he concluded that lid lag is the result of a disturbance in the innervation of the musculature of the lid. Müller's muscle, composed of unstriated fibers and innervated by sympathetic nerves, extends from the levator palpebrae superioris muscle to the upper border of the tarsus and regulates the movement of the lid.[14] It is purely an eyelid muscle, having no relation to the eyeball. It is apparent, therefore, that even though it plays an important role in the production of the symptoms of exophthalmic goiter affecting the eyelid it does not contribute to the exophthalmos. The demonstration that the lid lag is of nervous origin did, however, lend additional support to the concept that the syndrome of thyrotoxic goiter is caused by sympathetic stimulation.

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12. Bernard, C.: Leçons de physiologie expérimentale appliquie à la médecine, Paris, J. B. Bailliere, 1855.

13. von Graefe, A.: Ueber Basedow'sche Krankheit, Deutsche Klin. **16**:158-159 (April 16) 1864.

14. Müller, H.: Ueber einen glatten Muskel in der Augenhöhle des Menschen und der Saugethiere, Ztschr. f. wissensch. Zool. **9**:541 (Dec. 20) 1858.

Cannon, Binger and Fitz [15] approached this problem experimentally in 4 dogs by fusing the right phrenic nerve to the cervical portion of the sympathetic trunk on the right. As a result of this anastomosis a volley of impulses was relayed to the superior cervical ganglion every time the animal breathed. Five months later all 4 animals exhibited tachycardia, loss of weight, looseness of the bowels, excitability and an increase in the metabolic rate (50 to 150 per cent). Only 1 animal showed respiratory hippus, exophthalmos and enlargement of the pupil on the side operated on.

There is also clinical evidence, albeit indirect, which leads to suspicion of the sympathetic nervous system in the causation of exophthalmos and toxic goiter. The frequent sudden onset of the latter, particularly after emotional trauma, and the rapidity with which the clinical picture changes suggest a nervous element. Falta [16] was the first to note that the exophthalmos may also develop "in a few days or a single night." This could be explained only by a nervous mechanism, since it is difficult to believe that local pathologic changes would occur so quickly. Granted that such a nervous mechanism exists, how then does sympathetic stimulation produce the exophthalmos?

Landström [17] discovered a shallow cone of unstriated muscle in the human orbit supplied by sympathetic fibers. It arose anteriorly from the orbital fascia (septum orbitale) and extended posteriorly, with its insertion just beyond the equator of the eyeball. He stated the belief that this muscle was an antagonist to the four rectus muscles, which tend to pull the globus oculi inward. The exact role of Landström's muscle, however, is questionable, for Moore [6] was unable to find any evidence of this muscle in a study of several hundred human orbits. Furthermore, even if the muscle did exist, its contraction would result only in protrusion of the eye up to the septum orbitale because of the site of its attachment. Clinical observation shows that there are many patients in whom the exophthalmos is far greater than this.

Sappey,[18] basing his opinion on dissections of the human orbit, stated that the protrusion of the eyeball after stimulation of the cervical portion of the sympathetic trunk is caused by contraction of a fibromuscular cone, a part of the orbital aponeurosis. The base of this cone is firmly attached to the entire surface of the orbital margin and at this point is distinctly fibrous. The apex of the cone is attached to the margins of the optic foramen, the foramen orbitale and the foramen

15. Cannon, W. B.; Binger, C. A. L., and Fitz, R.: Experimental Hyperthyroidism, Am. J. Physiol. **36**:363-364 (March) 1915.

16. Falta, W.: Die Erkrankungen der Blutdrusen, Berlin, Julius Springer, 1913, p. 50.

17. Landström, J.: Ueber Morbus Basedowii, Stockholm, P. A. Norstedt & Söner, 1907, p. 161.

18. Sappey, T., cited by MacCallum and Cornell.[19]

rotundum, becoming denser and more muscular as it passes to its posterior insertion. Experimenting on anesthetized dogs, MacCallum and Cornell [19] exposed this fibromuscular cone of Sappey. During stimulation of the cervical sympathetic nerves the cone was observed to contract along its longitudinal axis, thus producing exophthalmos. When the cone was cut by a transverse section no exophthalmos appeared. Code and Essex,[20] confirming all the anatomic and physiologic findings of MacCallum and Cornell, further found that, although the fibromuscular cone is present in both human beings and dogs, it is not as well developed in the former. Nevertheless, they stated the belief that it is capable of producing exophthalmos. Recently, however, Essex and Corwin,[21] in studying the effects of anesthesia on the position of the eyeball in dogs, observed that hypnotics, such as sodium amytal, pentothal sodium and chloralose (a preparation of chloral hydrate and dextrose), produce enophthalmos (2 to 6 mm.). Stimulation of the cervical sympathetic nerves in dogs narcotized by such agents then produces "exophthalmos," but the eyeball has only returned to its original preanesthetic position. Brunton [22] reported that the administration of sympathomimetic drugs to unanesthetized dogs produces some exophthalmos (1 mm.). This effect, however, is slight and does not compare with the degree of proptosis evoked in narcotized dogs under the same circumstances. In the light of these experiments, the validity of the results obtained by stimulation of the cervical portion of the sympathetic nervous system of anesthetized animals must be seriously questioned.

It is highly improbable that exophthalmos can be produced in man by cervical sympathetic stimulation. All clinical experiments, performed on patients operated on for reasons other than exophthalmic goiter, failed to demonstrate the occurrence of exophthalmos following cervical sympathetic stimulation *when ocular protrusion was measured with an exophthalmometer.*[23] Jonnesco [24] reported exophthalmos following

19. MacCallum, W. G., and Cornell, W. B.: On the Mechanism of Exophthalmos, M. News **85**:732-736 (Oct. 15) 1904.

20. Code, C. F., and Essex, H. E.: The Mechanism of Experimental Exophthalmos, Am. J. Ophth. **18**:1123-1128 (Dec.) 1935.

21. Essex, H. E., and Corwin, W. C.: Experimental "Exophthalmos" in Dogs, Am. J. Ophth. **20**:153-157 (Feb.) 1937.

22. Brunton, C. E.: Studies in Exophthalmos: The Effects of Certain Sympathomimetic Substances on the Eye of the Cat and Dog, J. Physiol. **84**:334-341 (June 18) 1935.

23. Unverricht, W.: Experimentelle Untersuchungen über die Ursache des Exophthalmus, Klin. Wchnschr. **4**:878-879 (April 30) 1925. Mutch, J. R.: The Pupil After Cervico-Thoracic Sympathetic Ganglionectomy: Photographic Observations in Man, Edinburgh M. J. **43**:743-746 (Dec.) 1936. Pochin, E. E.: Ocular Effects of Sympathetic Stimulation in Man, Clin. Sc. **4**:79-89 (June) 1939.

24. Jonnesco, T.: La résection totale et bilatérale du sympathétique cervical (traitement du goître exophtalmique), Ann. d'ocul. **117**:161-175 (March) 1897.

cervical sympathetic stimulation in human beings, but the proptosis was observed and not measured. As cervical sympathetic stimulation produces lid lag, it is possible that this was interpreted as exophthalmos. Additional evidence is found in the fact that mydriasis is never present in the exophthalmos of thyrotoxic goiter but is always present after cervical sympathetic stimulation in both human beings and experimental animals.

There is some clinical evidence that minimizes the importance of the sympathetic nervous system in the production of exophthalmos. Brain [25] has reported the occurrence of thyrotoxic goiter with marked exophthalmos in a patient who had suffered from complete bilateral paralysis of the cervical nerves of fifteen years' duration because of syringomyelia. Surgical therapy, such as excision of the superior cervical ganglion or bisection of the cervical sympathetic chain, has been used in the treatment of persistent postoperative exophthalmos with little success. Despite occasional enthusiastic reports,[26] such neurosurgical procedures have been generally discarded.

ROLE OF THE THYROID GLAND

Superficial observation and a paucity of information frequently create the impression that the relation of the thyroid gland and exophthalmos in exophthalmic goiter is a simple one, i. e., cause and effect, the exophthalmos being, like the nervousness, tremor, increased basal metabolic rate and other signs and symptoms, merely another manifestation of thyroid hyperfunction. Nothing could be further from the truth. For example, Greenlee [27] recently reported on a patient with exophthalmic goiter in whom the only clinical and laboratory findings were slight nervousness and a basal metabolic rate that varied from + 7 to + 20 per cent but who had severe exophthalmos. Cattell [28] in an analysis of 800 cases of thyrotoxic goiter found that only 46 per cent of the patients had exophthalmos and that the appearance of this ocular sign did not parallel the severity of the thyrotoxicosis. Furthermore,

25. Brain, W. R.: Exophthalmos Following the Administration of Thyroid Extract, Lancet **1**:182-186 (Jan. 25) 1936.

26. Jonnesco, T.: The Enduring Results of Total Bilateral Resection of the Cervical Sympathetic in Basedow's Disease, Internat. Clin. **1**:136-148, 1903. Jaboulay, M.: Interventions sur le sympathique cervical et sur le corps thyroïde dans la maladie de Basedow, Lyon chir. **4**:225-230 (Sept. 1) 1910. Layani, F.; Welti, H., and Leven, R.: Exophthalmie Basedowienne unilatérale résiduelle, Bull. et mém. Soc. méd. d. hôp. de Paris **55**:1204-1211 (July 17) 1939.

27. Greenlee, D. P.: A Case of Exophthalmic Goiter, with Marked Eye Findings and Mild Constitutional Symptoms, Pennsylvania M. J. **43**:61-64 (Oct.) 1939.

28. Cattell, R. B.: The Eye Complications in Exophthalmic Goiter: Cataracts and Exophthalmos, Ann. Surg. **100**:284-303 (Aug.) 1934.

50.3 per cent of those patients who were successfully treated by thyroidectomy showed complete regression of the exophthalmos, 13.1 per cent partial retrocession and 21.7 per cent no improvement, and in 1.1 per cent progressive exophthalmos developed. In a recent review [29] of the reported cases of postoperative progressive exophthalmos, it was stated that only 1 of 80 patients showed an increased basal metabolic rate. Moreover, it is known clinically [30] that when the exophthalmos develops early in the course of the disease the protrusion is likely to be severe and resistant to therapy, whereas if it develops late thyroidectomy is most likely to give relief of the ocular symptoms regardless of the severity of the disease as a whole. In addition, toxic nodular goiter almost never results in exophthalmos, whereas toxic diffuse goiter frequently does.

On the other hand, some clinical data support the concept of a simple direct relation between thyroid substance and exophthalmos. Crotti [30] has reported the development of exophthalmos in 2 healthy volunteers who ingested huge amounts of thyroid substance within a few weeks. Furthermore, 10 cases [31] have been reported in which exophthalmos appeared after excessive thyroid therapy for obesity, and there are 6 published instances [32] in which proptosis occurred in patients with myxedema under similar circumstances. In these 16 cases the thyroid substance had been administered for more than a year. The occurrence of proptosis after the administration of excessive doses of thyroid substance in cases of obesity and of myxedema is probably rare, especially if one considers the frequency with which this therapeutic agent is prescribed, its easy availability and its possible misuse. It is noteworthy that this endocrine product has been used clinically for

29. Ginsburg, S.: Postoperative Progressive Exophthalmos, with Low Basal Metabolic Rate, Ann. Int. Med. **13**:422-450 (Sept.) 1939.

30. Crotti, A.: Diseases of the Thyroid, Parathyroids and Thymus, Philadelphia, Lea & Febiger, 1938.

31. von Notthafft, A. F.: Ein Fall von artificiellem akutem thyreogenem Morbus Basedow, Centralbl. f. inn. Med. **19**:353-379 (April 16) 1898. Holbøll, S. A.: A Fatal Case of Exophthalmic Goiter, Ugesk. f. læger **89**:916-917 (Oct. 6) 1927. Møller, E.: A Fatal Case of Exophthalmic Goiter Commenced During Thyroid Gland Administration, Acta med. Scandinav. **73**:1-9, 1930. Hurxthal, L. M.: Exophthalmic Goiter Following the Use of Thyroid Extract or Diet for Reduction of Weight, S. Clin. North America **11**:441-443 (April) 1931.

32. Béclère, M.: Thyroïdisme—ses rapports avec la maladie de Basedow et l'hystérie, Gaz. méd. de Paris **1**:499 (Oct. 20) 1894. Lawford, J. B.: Experimental Exophthalmos and Enophthalmos, Lancet **1**:310-311 (Feb. 3) 1900. Ulrich, C.: Ueber Morbus Basedowii und Myxödem, Therap. Monatsh. **14**:291-295 (June) 1900. Stegman, R.: Zur Behandlung des Morbus Basedowii mit Röntgenstrahlen, Wien. klin. Wchnschr. **19**:62-63 (Jan. 18) 1906. Møller, E.: Uebergang des Myxödems in Morbus Basedowii, Deutsche med. Wchnschr. **56**:1699-1700 (Oct. 3) 1930. Moorhead, T. G.: Unilateral Exophthalmos Following the Administration of Thyroid Extract, Brit. M. J. **1**:442-443 (March 14) 1931.

over fifty years and that fewer than 20 such cases have been reported in the literature.

The results of animal experiments are likewise inconclusive. Many authors [33] have demonstrated that the administration of thyroid gland extracts to dogs, rabbits and monkeys reproduces the whole syndrome of exophthalmic goiter, including exophthalmos. On the other hand, Carlson [34] and Kunde [35] were unable to produce exophthalmos in dogs by means of thyroid extracts even though the other symptoms of hyperthyroidism were constantly present. The latter author, however, stated that if the animals were first rendered myxedematous by thyroidectomy, administration of large doses of thyroid substance would produce exophthalmos. Gley [36] noted spontaneous exophthalmos in rabbits after thyroidectomy. Klose [37] gave dogs injections of *Presssaft* (pressed juice) from thyrotoxic goiters removed at operation and produced all the symptoms of exophthalmic goiter, including proptosis, whereas extracts of nontoxic goiters were entirely ineffective.

Prolonged feeding of cabbage to rabbits can produce thyroid hyperplasia.[38] The active agent is believed to be the cyanides present in the cabbage. Marine [39] injected various cyanides daily into rabbits maintained on a nongoitrogenic diet of alfalfa hay, oats and tap water and thereby produced thyroid hyperplasia. Of the various cyanides used, methyl cyanide proved most potent, daily injections of 0.1 cc. producing bilateral proptosis as early as the twentieth day after the first injection.[40] However, the percentage of successes was moderate because

33. Edmunds, W.: Experimental Exophthalmos and Enophthalmos, Tr. Ophth. Soc. U. Kingdom **20**:243-254, 1900. Kraus, F., and Friedenthal, H.: Ueber die Wirkung der Schilddrüsenstoffe, Berl. klin. Wchnschr. **45**:1709-1714 (Sept. 21) 1908. Baruch, M.: Zur experimentellen Erzeugung des Morbus Basedowii, Zentralbl. f. Chir. **39**:316-317 (March 9) 1912.

34. Carlson, A. J.; Rooks, J. R., and McKie, J. F.: Attempts to Produce Experimental Hyperthyroidism in Mammals and Birds, Am. J. Physiol. **30**:129-159 (April) 1912.

35. Kunde, M. M.: Studies on Metabolism: Experimental Hyperthyroidism, Am. J. Physiol. **82**:195-215 (Sept.) 1927.

36. Gley, E.: De l'exophthalmie consécutive à la thyroïdectomie, Présentation d'animaux, Compt. rend. Soc. de biol. **68**:858-862, 1910.

37. Klose, H.: Die Chirurgie der Basedowschen Krankheit, in Neue deutsche Chirurgie, Stuttgart, Ferdinand Enke, 1929, vol. 44, p. 62.

38. Chesney, A. M.; Clawson, T. A., and Webster, B.: Endemic Goiter in Rabbits: Incidence and Characteristics, Bull. Johns Hopkins Hosp. **43**:261-277 (Nov.) 1928.

39. Marine, D.; Bauman, E. J.; Spence, A. W., and Cipra, A.: Further Studies on the Etiology of Goiter with Particular Reference to the Action of Cyanides, Proc. Soc. Exper. Biol. & Med. **29**:773-775 (March) 1932.

40. Marine, D.; Spence, A. W., and Cipra, A.: Production of Goiter and Exophthalmos in Rabbits by the Administration of Cyanide, Proc. Soc. Exper. Biol. & Med. **29**:822-823 (April) 1932.

the exophthalmos appeared only in young animals showing marked thyroid hyperplasia. Two strains of rabbits were used, one strain being decidedly more susceptible to the methyl cyanide. The animals became nervous and diarrhea developed as the ocular protrusion appeared. Although the basal metabolic rates were not taken, it was believed that the condition of these animals simulated the clinical picture of exophthalmic goiter in man. When the experimental animals were first thyroidectomized, the percentage of response to the methyl cyanide was doubled. Furthermore, thyroxin and desiccated thyroid substance effectively prevented the methyl cyanide from evoking exophthalmos in both the intact and the thyroidectomized rabbits.[41]

Additional evidence of the antagonism of thyroid substance and experimental exophthalmos was noted by Smelser.[42] He observed that the production of exophthalmos in guinea pigs by injections of anterior pituitary extract is significantly increased if the animals have been thyroidectomized and, conversely, that the administration of desiccated thyroid substance to thyroidectomized guinea pigs tends to prevent the occurrence of exophthalmos.

ROLE OF THE ANTERIOR LOBE OF THE PITUITARY GLAND

It has been demonstrated that injections of acid extracts of the anterior lobe of the pituitary gland can produce thyroid hyperplasia and exophthalmos in ducks[43] and young guinea pigs.[44] Friedgood[45] observed that the basal metabolic rate of guinea pigs increased at first and then returned to normal despite the continued injection of anterior pituitary substance. In some animals, slight protrusion appeared when the thyroid activity was maximum, but "striking exophthalmos was seen only in those animals which were injected over a period of several months and especially in those which finally developed abnormally low basal metabolic rates." Friedgood therefore concluded that the hypo-

41. Marine, D.; Rosen, S. H., and Cipra, A.: Further Studies on Exophthalmos in Rabbits Produced by Methyl Cyanide, Proc. Soc. Exper. Biol. & Med. **30**:649-651 (Feb.) 1933.

42. Smelser, G. K.: Treatment of Experimentally Produced Exophthalmos with Thyroxin and Other Iodine Compounds, Am. J. Ophth. **21**:1208-1218 (Nov.) 1938.

43. Schoeckaert, J. A.: Enlargement and Hyperplasia of Thyroids in Young Ducks from Injections of Anterior Pituitary, Proc. Soc. Exper. Biol. & Med. **29**: 306-308 (Dec.) 1931.

44. Loeb, L., and Friedman, H.: Exophthalmos Produced by Injections of Acid Extract of Anterior Pituitary Gland of Cattle, Proc. Soc. Exper. Biol. & Med. **29**: 648-650 (Feb.) 1932.

45. Friedgood, H. B.: Experimental Exophthalmos and Hyperthyroidism in Guinea Pigs: Clinical Course and Pathology, Bull. Johns Hopkins Hosp. **54**: 48-73 (Jan.) 1934.

thyroid state, rather than the hyperthyroid state, is conducive to the production of such exophthalmos. Subsequently other authors [46] found that exophthalmos occurs less frequently and to a lesser degree in intact animals than in thyroidectomized animals.

The mechanism by which anterior pituitary substance produces thyroid hyperplasia and ocular protrusion has not yet been settled. Marine [47] has found that in those animals in which exophthalmos was produced by preliminary thyroidectomy and subsequent injection of methyl cyanide, the anterior lobe of the pituitary gland was consistently hypertrophied and the stainable acidophile cells were either decreased in number or were absent. The decrease in the stainable acidophile cells and the hypertrophy of the pituitary gland are believed to indicate increased secretory function. These changes in the anterior lobe of the pituitary gland were inhibited by the administration of desiccated thyroid substance. As stated previously, bisection of the cervical sympathetic nerves also inhibited exophthalmos. Marine suggested that methyl cyanide activated anterior pituitary secretion which in turn produced exophthalmos by sympathetic stimulation via a hypothetic sympathetic brain center. He [48] concluded that the production of exophthalmos by injections of either methyl cyanide or an anterior pituitary extract potent in the thyrotropic hormone depends on the same mechanism, namely, increased circulation of thyrotropic hormone in the presence of a relative or absolute thyroid deficiency.

Smelser,[46] on the other hand, denied the sympathetic nervous system any role whatever. He found that injections of anterior lobe extract in thyroidectomized guinea pigs previously subjected to a unilateral cervical ganglionectomy produced bilateral exophthalmos. Although the exophthalmos on the ganglionectomized side was less than on the side not operated on, it was greater than that of the controls operated on. Examination of the orbital contents of the experimental animals revealed an increase in the weight of the retrobulbar tissue [49] as follows: fatty connective tissue, 100 per cent; dorsal lacrimal gland, 40 per cent, and

46. (*a*) Smelser, G. K.: Experimental Production of Exophthalmos Resembling That Found in Graves' Disease, Proc. Soc. Exper. Biol. & Med. **35**:128-130 (Oct.) 1936. (*b*) Paulson, D. L.: Experimental Exophthalmos in the Guinea Pig, ibid. **36**: 604-605 (June) 1937. (*c*) Aird, R. B.: Experimental Exophthalmos and Associated Myopathy Induced by Thyrotropic Extract, Arch. Ophth. **24**:1167-1178 (Dec.) 1940.

47. Marine, D., and Rosen, S. H.: Exophthalmos in Thyroidectomized Guinea Pigs by Thyrotropic Substance of the Anterior Pituitary, and the Mechanism Involved, Proc. Soc. Exper. Biol. & Med. **30**:901-903 (April) 1933.

48. Marine, D., and Rosen, S. H.: The Exophthalmos of Graves' Disease: Its Production and Significance, Am. J. M. Sc. **188**:565-571 (Oct.) 1934.

49. Smelser, G. K.: Histology of the Orbital and Other Fat Tissue Deposits in Animals with Experimentally Produced Exophthalmos, Am. J. Path. **15**:341-352 (May) 1939.

extraocular muscles, 22 per cent. The augmentation in weight of the tissues was as great on the side operated on as it was on the side not operated on. Histologic examination of the fatty connective tissue from the orbital, cervical, axillary, renal and pelvic regions revealed changes similar although differing in degree, the orbital region showing the most. Edema and wandering cell infiltration were constant findings and were also most severe in the orbit. It was further noted that the retrobulbar changes were unaffected either by excision of Müller's muscle or by orbital decompression.[50] Paulson[51] confirmed these findings and, in addition, noted that the mean percentage increase in the water content of the retrobulbar tissue, exclusive of the lacrimal gland, was as much as 6 per cent. Smelser[10] concluded that these histologic changes in the guinea pig were identical with those he had found in patients with progressive post-thyroidectomy exophthalmos. On the other hand, Aird,[46c] using the same experimental procedure, reported that the retrobulbar tissues appeared normal except for slight edema and concluded that the exophthalmos was probably caused by an increase in the size of the extraocular muscles. Histologic examination of the muscles revealed slight degenerative changes, interstitial edema and round cell infiltration. These changes are similar to those observed by Naffziger[11] in his patients with "malignant" exophthalmos.

Investigations of the excretion of thyrotropic hormone in the urine of healthy persons and of patients with thyroid disease have produced conflicting results.[52] Antognetti and Geriola[52d] failed to demonstrate

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50. Smelser, G. K.: Role of the Cervical Sympathetic Ganglia and Müller's Orbital Muscle in Experimental Exophthalmos, Am. J. Ophth. **22**:1201-1209 (Nov.) 1939.

51. Paulson, D. L.: Experimental Exophthalmos and Muscle Degeneration Induced by Thyrotropic Hormone (Antuitrin-T, Pituitary Extract), Proc. Staff Meet., Mayo Clin. **14**:828-832 (Dec. 27) 1939.

52. (*a*) Aron, M., and Klein, M.: Sur la présence, dans l'urine humaine, d'une substance douée de la même action sur la thyroïde que l'extract préhypophysaire, et sur l'interprétation de la réaction de diagnostic de la grossesse, Compt. rend. Soc. de biol. **103**:702-704, 1930. (*b*) Krogh, M., and Okkels, H.: L'hormone thyréostimulante préhypophysaire est-elle présente dans l'urine? ibid. **113**:635-638, 1933. (*c*) Smith, M., and Moore, E.: Is Anterior Pituitary Hormone Demonstrable in the Urine of Graves' Disease or in the Urine of Guinea Pigs Injected with Anterior Pituitary Extract? Proc. Soc. Exper. Biol. & Med. **30**:735-739 (March) 1933. (*d*) Antognetti, L., and Geriola, F.: Studi sui "tests" ormonici; l'ormone tireotropo preipofisario, Endocrinol. e pat. costit. **11**:395-410 (July) 1936. (*e*) Hertz, S., and Oastler, E. G.: Assay of Blood and Urine for Thyreotropic Hormone in Thyrotoxicosis and Myxedema, Endocrinology **20**:520-525 (July) 1936. (*f*) Thompson, K. W.: The Non-Specificity of Thyreotropic Antihormone, Proc. Soc. Exper. Biol. & Med. **35**:637-640 (Jan.) 1937. (*g*) Cope, C.: The Anterior Pituitary Lobe in Graves' Disease and Myxedema, Quart. J. Med. **7**:151-170 (Jan.) 1938. (*h*) Emerson, K., Jr., and Cutting, W. C.: Urinary Thyreotropic Hormone, Endocrinology **23**:439-445 (Oct.) 1938.

the hormone in the urine of controls or of patients with thyroid disease, although Aron and Klein [52a] reported the presence of thyrotropic activity in the urine of both normal persons and patients with hyperthyroidism. However, the weight of evidence indicates that the thyrotropic hormone, a principle not excreted in the urine of normal healthy controls, is only occasionally found in cases of hyperthyroidism, is frequently recovered in cases of spontaneous myxedema and is most constantly present in the urine after thyroidectomy. Emerson and Cutting [52b] noted thyrotropic activity in the urine of 7 of 11 patients with thyrotoxic goiter postoperatively but found the level of excretion unrelated to the degree of hypothyroidism.

In conclusion it may be stated that the evidence clearly suggests a cause and effect relation between the thyrotropic hormone and postthyroidectomy exophthalmos and that the effectiveness of the hormone is enhanced by a relative insufficiency of thyroid secretion. However, as only 1 per cent of thyroidectomized patients have progressive exophthalmos, some unknown factor must be involved.

POSSIBLE ROLE OF THE GONADS

Marine stated, as previously noted, that his success in producing experimental exophthalmos was dependent on the age of the rabbits—the very young and the adult animals responded poorly to methyl cyanide, whereas the prepubertal animals were most sensitive. Moreover, exophthalmic goiter is typically a disease of young adults, about 60 per cent of the patients being less than 40. Marine and Rosen [53] observed that the incidence of exophthalmos produced by methyl cyanide in intact and in thyroidectomized rabbits was always greater in the males. If the animals were first gonadectomized and then given injections no exophthalmos appeared. Conversely, gonadectomy caused the regression of any preexisting proptosis. The administration of estrogen, chorionic gonadotropin (follutein) or epinephrine did not affect these results. Cryptorchidism had neither an inhibiting nor a stimulating influence.[54] The androgens (testosterone proprionate, androsterone and dehydroandrosterone) when injected into rabbits produced or increased the exophthalmos only if the animals had had exophthalmos and had recovered, had latent proptosis or already had definite exophthalmos. Thyroid substance inhibits this effect of the

53. Marine, D., and Rosen, S. H.: The Influence of the Gonads on Exophthalmos in Rabbits, Proc. Soc. Exper. Biol. & Med. **35**:354-356 (Nov.) 1936.

54. Marine, D., and Rosen, S. H.: The Effects of Cryptorchidism and Castration on Exophthalmos in Rabbits and Guinea Pigs, Am. J. Physiol. **121**:620-624 (March) 1938.

androgens.[55] At present no analysis of the excretion of androgen by patients suffering from exophthalmic goiter is available. However, while it is true that the majority of patients with postoperative progressive exophthalmos are male, exophthalmic goiter occurs much more frequently in women, thus invalidating any implication of preponderance in males. There is not sufficient evidence at present to warrant any conclusion concerning the relation, if any, of androgens to exophthalmos.

SUMMARY

1. Postmortem examinations, observations made at decompression operations and biopsy studies of the orbital contents of patients with postoperative progressive exophthalmos indicate that an increase in both the weight and the volume of the fatty connective tissue and the extraocular muscles is a constant local pathologic finding. Histologically, hypertrophy of the fat and parenchymatous degeneration and fibrosis of the muscles, as well as edema and round cell infiltration of both structures, are present. It is concluded, therefore, that "malignant" exophthalmos results from mechanical pressure due to the increased volume of the ocular fatty connective tissue and of the extraocular muscles.

Identical intraorbital changes can be produced in laboratory animals by repeated injections of extracts containing the thyrotropic hormone of the anterior lobe of the pituitary gland. This technic is most successful if the animals are first thyroidectomized. As excessive excretion of the thyrotropic hormone is found typically in the urine of thyroidectomized patients and as patients with malignant exophthalmos typically have low metabolic rates, it is strongly suggested that post-thyroidectomy progressive exophthalmos is caused by an increased secretion of thyrotropic hormone produced in patients in the hypothyroid state.

2. The causation of reversible, nonprogressive exophthalmos, the type most commonly seen in patients with exophthalmic goiter is not known. No pathologic examination of the orbital contents prior to operation has ever been reported. The local etiologic agent is not known. Contractions of various sets of muscle fibers within the orbit, muscles innervated by the cervical sympathetic nerves, have been suggested as the mechanism. However, while it has been demonstrated that cervical sympathetic stimulation can produce proptosis in animals, it has also been shown that the use of anesthesia produces effects which invalidate the results obtained. Until cervical sympathetic stimulation is conducted in unanesthetized animals, the question of whether or not exophthalmos can be produced in animals by stimulation of sympa-

55. Marine, D.: The Effect of Androgens on Exophthalmos in Rabbits, Proc. Soc. Exper. Biol. & Med. **38**:353-356 (April) 1938.

thetic nerves will remain unsettled. Furthermore, all carefully conducted attempts to produce proptosis in human being by this technic have failed.

The relation of the thyroid gland to this type of exophthalmos is also not known. The weight of evidence suggests that the administration of thyroid substance cannot produce exophthalmos, although there are some experimental results to the contrary. However, the following statement seems to be true. If an animal is first thyroidectomized, the administration of excessive doses of thyroid extract can produce proptosis. There are also a few reports of healthy obese and of myxedematous patients having exophthalmos after excessive thyroid therapy. How these several observations are related to the exophthalmos of exophthalmic goiter is still a matter for conjecture.

Questions and Answers

COMPENSATION FOR OCULAR DISABILITY

To the Editor:—How is the compensable disability estimated after injury when it is necessary for glasses to be used to improve vision, especially after removal of traumatic cataract? Is disability estimated with or without correcting lenses?

A. R. C., M.D.

Answer.—In most states the loss of binocular single vision is considered the total loss of use of one eye. If binocular vision can be restored, the amount of disability depends on the law of the particular state. State laws are not identical. In some states all tests of acuity are made without glasses; in some they are made with glasses, and in some a compromise is provided.

See the report of the Committee on Visual Economics of the Section on Ophthalmology of the American Medical Association (*J. A. M. A.* **115:** 368-369 [Aug. 3] 1940).

News and Notes

EDITED BY DR. W. L. BENEDICT

GENERAL NEWS

Postgraduate Lectures in Ophthalmology.—The following postgraduate lectures in ophthalmology will be given at the Tennent Institute of Ophthalmology, Glasgow, Scotland: April 8, "Dark Adaptation," by Professor Riddell; April 15, "Ophthalmic Dermatology," by Dr. Herbert Brown; April 22, "Pathologic Problems," by Dr. James Hill, and April 29, "Vestibular Nystagmus," by Dr. Tom Howie.

These lectures are open to any medical members of the allied forces who care to attend, and visitors will be welcome in the department at any time.

SOCIETY NEWS

Association for Research in Ophthalmology.—A meeting of the Association for Research in Ophthalmology will be held at the Marlborough-Blenheim Hotel, in Atlantic City, N. J., June 9, 1942. The following papers are scheduled for presentation:

At 9:30 a. m.: "A Quantitative Study of the Cells and Fibers in the Nucleus Nerve Complexes of the Fourth and Sixth Cranial Nerves," Robison D. Harley, M.D., Ph.D., the Mayo Clinic, Rochester, Minn.; "The Intrascleral Vascular Plexus and Its Relations to the Aqueous Outflow," Manuel U. Troncoso, M.D., the Presbyterian Hospital, New York; "Corneal Permeability: I. Factors Affecting Penetration of Drugs into the Cornea," Kenneth C. Swan, M.D., and Norman G. White, M.S., State University of Iowa, Iowa City, and "Fibroblastic Overgrowth of Persistent Tunica Vasculosa Lentis in Infants Born Prematurely: III. Studies in Development and Involution of the Hyaloid Artery and Tunica Vasculosa Lentis," T. L. Terry, M.D., Massachusetts Eye and Ear Infirmary, Boston.

At 2:30 p. m.: "Gonioscopic Studies on the Canal of Schlemm," Peter C. Kronfeld, M.D., H. Isabelle McGarry, M.D. and Homer E. Smith, M.D., the Illinois Eye and Ear Infirmary, Chicago; "Some Observations and Experimental Studies on the Physiology of the Ciliary Muscle," Erich Sachs, M.D., Wayne University College of Medicine, Detroit; "Sulfadiazine Iontophoresis in the Treatment of Pyocyaneous Infection of the Rabbit Cornea," Ludvig von Sallmann, M.D., Department of Ophthalmology of Columbia University College of Physicians and Surgeons, New York, and "The Aqueous Veins: Physiologic Importance of the Visible Elimination of the Intraocular Fluid," K. W. Ascher, M.D., University of Cincinnati, Cincinnati.

Further information may be procured from the Secretary-Treasurer, Dr. C. S. O'Brien, University Hospitals, Iowa City.

Brazilian Board of Ophthalmology.—A Brazilian Board of Ophthalmology (Conselho Nacional de Ophthalmologia) has been definitely established, and the officers were elected on January 16. According to

its by-laws, ophthalmologists who can prove themselves capable of fulfilling a certain number of requisites will be certified. This system will be in effect until June 1942. After that certificates will be given only to those who have passed an examination. Examinations will be held for the first time in June, and they will be held regularly every year in that month. The requisites for taking the examinations are more or less the same as those used in the United States.

Eye, Ear, Nose and Throat Section of the New York State Medical Society.—The section will meet at the Waldorf-Astoria, New York city, April 28. The following papers will be presented: "A New Approach to Cross Cylinder Tests," Joseph I. Pascal, M.D., New York; "Tangent Screen Scotometry in Office Practice," Walter F. Duggan, M.D., Utica, N. Y. (discussion, John N. Evans, M.D., Brooklyn); "Common Anomalies and Their Treatment," Virgil Casten, M.D., Boston (discussion, John H. Dunnington, M.D., New York); "A Treatment for Herpes Zoster Ophthalmicus," Walter I. Lillie, M.D., Philadelphia (discussion, Ralph I. Lloyd, M.D., Brooklyn), and "Sulfanilamide and Its Derivatives in Ophthalmology," Phillips Thygeson, M.D., and William Stone Jr., M.D., New York (discussion, L. Maxwell Lockie, M.D., Buffalo, N. Y.).

Reading (Pa.) Eye, Ear, Nose and Throat Society.—The society held its ninth meeting at the Wyomissing Club March 18. It was addressed by Dr. Joseph C. Yaskin on "Diseases of Some of the Cranial Nerves as Related to Eye, Ear, Nose and Throat Conditions."

Obituaries

CASEY ALBERT WOOD, M.D.

1856–1942

Dr. Casey Albert Wood died January 26 at the Scripps Metabolic Clinic, in La Jolla, Calif., eight weeks after a cerebral accident. A private funeral was held in La Jolla, and later his ashes will be interred in the Mount Royal Cemetery in Montreal, Canada.

Dr. Wood was born of American parents in Wellington, Ontario, Canada, on Nov. 21, 1856. He was educated in private schools and was graduated from the Ottawa Collegiate Institute in 1874.

At University Bishop's College he received the degrees of master in surgery and doctor of medicine in 1877 and of doctor of civil law in 1903. McGill University conferred on him in 1906 the degree of doctor of medicine and in 1921 the degree of doctor of laws.

His early training in ophthalmology was taken at the New York Eye and Ear Infirmary and Post-Graduate Medical School in 1886. Courses at many European clinics followed, and in the years 1888 and 1889 he served as assistant surgeon in several London clinics.

Dr. Wood was married in 1886 to Emma Shearer, of Montreal, Canada, who survives him. In 1890 he located in Chicago, where he served as attending ophthalmic surgeon on the staffs at Alexian Brothers', Passavant Memorial and St. Luke's hospitals.

He served as professor of ophthalmology on the faculties of the Chicago Post-Graduate Medical School, College of Physicians and Surgeons (Chicago) and Northwestern University Medical School.

Dr. Wood retired from practice in 1917 and was commissioned as major in charge of the ophthalmic department at Camp Sherman, Ohio. Later he was made Lieutenant Colonel on the Surgeon General's staff in Washington, D. C., where he worked with Col. Fielding Garrison on the history of World War I. He retired with the rank of colonel in the Medical Reserve, United States Army.

He served as president of the American Academy of Ophthalmology and Otolaryngology and of the Chicago Ophthalmological Society and as chairman of the Section on Ophthalmology of the American Medical Association. He was a founding fellow of the American College of Surgeons and of the Institute of Medicine of Chicago.

From 1894 to 1901 he served as editor in chief of the *Annals of Ophthalmology,* and from 1902 to 1908 he held the same position on the *Ophthalmic Record*. The latter journal was merged with others to

form the *American Journal of Ophthalmology,* and he served the new publication as editor in chief from 1908 to 1914.

As an author Dr. Wood enjoyed international recognition. He published many short articles in his special field as well as many translations of treatises on the eye. He has to his credit a number of

CASEY ALBERT WOOD, M.D.
1856-1942

textbooks on ophthalmology; "Common Diseases of the Eye," with T. A. Woodruff; "A System of Ophthalmic Therapeutics"; "A System of Ophthalmic Operations," and "The American Encyclopedia of Ophthalmology."

After World War I Dr. Wood spent two years in British Guiana studying the eyes of birds and reptiles. During the succeeding years he pursued his studies in various countries of the Far East. Thereafter until two years ago he resided in Rome, Italy, where he worked in the Vatican Library. There he was able to command the services of scholars who assisted in the translation of many foreign language works on ophthalmology.

His collection of books on ornithology and his medical library, together with rare books on ophthalmology collected during his travels, were given to McGill University, Montreal, Canada.

Dr. Wood's interests were worldwide, and he was a member of literary and scientific clubs and organizations in many of the principal cities throughout the world.

One may say of Dr. Wood, as was said of Lincoln, "There Was a man." A tremendous worker, he was always a stimulating, sympathetic friend.

His family and many friends should find comfort in their grief in that after a long useful life he was spared an unhappy invalidism at the last.

FRANK BRAWLEY.

Abstracts from Current Literature

EDITED BY DR. WILLIAM ZENTMAYER

Cornea and Sclera

A CASE OF CORNEAL ULCER ASSOCIATED WITH LYMPHOGRANULOMA VENEREUM. G. P. MEYER and J. REBER, Am. J. Ophth. **24:** 161 (Feb.) 1941.

Meyer and Reber report a case of corneal ulcer in a 29 year old Negro woman referred by the proctologic department, where a diagnosis of venereal lymphogranuloma had been made. Despite treatment the ulcer progressed. The Frei reaction was then found to be positive, and with the use of sulfanilamide the ulcer healed completely in two weeks.

W. S. REESE.

SULPHONAMIDE TREATMENT OF HYPOPYON ULCER OF THE CORNEA. I. L. JOHNSTONE, Brit. M. J. **1:** 887 (June 14) 1941.

The value of sulfanilamide and its derivatives in the treatment of ophthalmia neonatorum is definite. The present article is a record of clinical experiments with hypopyon ulcer beginning in June 1939 with sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) as a 0.7 per cent solution in isotonic saline solution used as eye drops. The results were encouraging without being phenomenal. They were a little better than those obtained with the usual antiseptics or optochin. The patients treated with sulfapyridine drops had the advantage of quicker recovery and less dense scarring. In some cases subconjunctival injections were also given, and in a number of cases sulfapyridine was given orally instead of or in addition to the drops.

During the previous few months a number of cases of severe involvement were observed, and it became evident that only by frequent instillation of the drops could the condition be controlled. In cases in which a continuous drip seemed necessary the use of sulfapyridine powder was tried. By this means the ulcer in 3 cases was healed. Subconjunctival injections of 10 per cent soluseptasine (disodium p-[γ-phenylpropylamino]-benzenesulfonamido-α-γ disulfonate) were given in a small number of cases in which there was no apparent discharge from the eye and conjunctical redness was moderate.

In addition to a sulfanilamide derivative, every patient had atropine and had some form of cautery applied to the ulcer. It is true that some eyes are cured by these means alone, but many eyes have resisted every form of treatment. It may be possible to omit the cautery when sulfanilamide or a derivative is used.

In the light of experience the author suggests the following outline of treatment: In addition to the patient's remaining in the hospital, atropine should be given, a cautery should be used and a smear and material for culture should be taken; in the absence of purulent discharge,

subconjunctival injections of 10 per cent soluseptasine or 0.07 per cent sulfapyridine should be given at two or three depots, about 5 minims (0.3 cc.) to each depot. When the organism is known the appropriate sulfanilamide compound should be chosen. For the pneumococcus, sulfapyridine powder should be dusted lightly over the cornea three times a day. For the streptococcus, sulfanilamide powder may be used or soluseptasine given as drops or by subconjunctival injection. For Staphylococcus aureus, sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) would seem to be the appropriate drug; in this experiment a 0.1 per cent solution in 1.4 per cent saline solution was used as drops, but no definite opinion can yet be offered regarding its superiority over sulfapyridine.

Fine powder, 200 mesh, causes no discomfort to the patient, though considerable conjunctival redness appears. It is well to precede the dusting of the cornea with one drop of 1 per cent decicaine.

ARNOLD KNAPP.

Conjunctiva

IMPOSSIBILITY OF CLOSE GENETIC RELATIONS BETWEEN MACROCORNEA OR MEGALOCORNEA AND HYDROPHTHALMOS. B. KAYSER, Klin. Monatsbl. f. Augenh. **102:** 11 (Jan.) 1939.

Kayser discusses the definition and etiology of macrocornea and megalocornea, citing the views of Theil, Peters and other authors on this subject. Kayser bases his discussion on a paper by vom Hofe (*Klin. Monatsbl. f. Augenh.* **101:** 105 [July] 1938). Disagreeing with vom Hofe, Kayser concludes that close genetic relations between macrocornea and hydrophthalmos do not exist and that vom Hofe failed to prove that macrocornea actually existed in the cases he described. Macrocornea and megalocornea are genuine primary anomalies of growth; they have nothing to do with disease. Moreover, their formation differs from that of hydrophthalmos; in macrocornea and megalocornea there is enlargement of the anatomic structures, while in hydrophthalmos there is narrowing. Anatomic findings are contradictory to vom Hofe's contention. Macrocornea and megalocornea are fetal "anlages" in the same area of the anterior segment of the globe in which the "anlages" of hydrophthalmos are located. It is impossible for two typically different "anlages" to occur simultaneously at the same area. The enlargement of the cornea in the families with hydrophthalmos described by vom Hofe can be explained uncontestably as secondary consequences of fetal hydrophthalmos which recurred after initial cessation.

K. L. STOLL.

Experimental Pathology

OCULAR CHANGES DUE TO SODIUM ACETARSONE. G. SALA, Ann. di ottal. e clin. ocul. **67:** 208 (March) 1939.

A review of the literature shows a fair number of reports indicating damage to the optic nerve by acetarsone. The drug belongs to the group of pentavalent arsenicals, from which damage to the nerve has been noted with much more frequency than from trivalent arsensicals. The author employed sodium acetarsone in rabbits. A dose of 0.046 Gm. per kilogram of body weight was found to be tolerated by most animals,

about double the dose by weight usually employed in practice. Intravenous injections were usually given every two days, ranging in amount from 0.1 to 0.8 Gm. per dose, total amounts of 9.2 to 18.1 Gm. being employed. In addition, 2 animals were given 300 to 400 Gm. of alcohol. The treatment was continued for two to five months. When toxic symptoms, especially tremor, appeared, the animals were killed, and the globes and nerves up to the chiasm were examined histologically. Lesions were observed in the retina of all 6 animals. The ganglion cell layer was particularly affected, with degeneration and complete disappearance of many cells. Other layers, especially the nerve fiber layer and internal plexiform and granular layers, also showed marked degeneration in certain animals. The changes varied, being more marked in the animals which received the larger doses. The changes were most marked in the equatorial region, becoming less so near the nerve. All animals showed evidence of diffuse degeneration of the optic nerve fibers. No difference was observed between the changes due to alcohol plus acetarsone and those due to acetarsone alone. Since the animals were otherwise free from disease, the changes found must be imputed to the effect of the arsenical alone.

S. R. GIFFORD.

General Diseases

OCULAR LESIONS OF BESNIER-BOECK-SCHAUMANN DISEASE. L.-M. PAUTRIER, Arch. d'opht. **2**: 689 (Aug.) 1938.

The characteristic histologic change of this disease, whether the lesion is in the skin, lymph nodes, bones or viscera, is an infiltration of epithelioid cells surrounded and intermingled with lymphocytes. The author calls attention to 3 cases of Heerfordt's disease in which there were also general lesions of Boeck's disease. He reviews the similarities between the two conditions and says that he is himself convinced that they are the same disease. The causation is still to be determined. This report should be read in the original.

S. B. MARLOW.

Glaucoma

SYMPTOMS SIMULATING GLAUCOMA IN A CASE OF CHORDOMA OF THE CLIVUS OF BLUMENBACH. H. MOLLER, Acta ophth. **17**: 20, 1939.

A diagnosis of glaucoma is not warranted on the basis of atrophy of the optic nerve, cupping and typical glaucomatous changes in the visual field, e. g., Bjerrum scotomas. The case reported illustrates this. A woman of 49 showed all of the foregoing characteristic features of glaucoma, but careful tonometric examination never revealed any increased intraocular tension. Roentgenographic and ventriculographic studies revealed changes indicative of a neoplasm in the region of the sella turcica. A chordoma of the basilar groove of the sphenoid bone was successfully removed at operation. By pressure on the optic nerves it had produced the atrophy. The excavation of the nerve heads was thought to be the result either of secondary retraction or of deficient resistance of atrophic tissue. The scotomas were produced, as in ordinary glaucoma, by the folding of nerve fibers over the borders of the excavated disks.

O. P. PERKINS.

Injuries

OPHTHALMIC CASUALTIES RESULTING FROM AIR RAIDS. D. R. CAMPBELL, Brit. M. J. **1**: 966 (June 28) 1941.

Observation of approximately 100 cases led to the classification of injuries from air raids according to the following causes: (1) incendiary bombs, (2) blasts and (3) direct blows. The effect of an incendiary bomb is that of multiple foreign bodies, burns of the lids and softening of the ocular tissues. The effect of blasts, that is sudden compression and expansion of the atmosphere, is proptosis from retrobulbar hemorrhage with immediate total loss of vision and subsequent optic nerve atrophy, extensive intraocular hemorrhage and ruptures at the macula with loss of central vision. Acute iritis and acute secondary glaucoma occurred in several cases a week after the injury. The patients were slow to recover. The direct blows caused perforating injuries of the cornea and rupture of the sclera, and frequently the eye had to be removed. There were several cases of severe traumatic keratitis, with which there were always associated contusion changes in the retina. Several penetrating wounds of the orbit occurred which healed without any complications. There were no cases of intraocular foreign bodies.

ARNOLD KNAPP.

Lacrimal Apparatus

TWO STAGE DACRYOCYSTORHINOSTOMY. Z. NIŽETIĆ, Klin. Monatsbl. f. Augenh. **102**: 71 (Jan.) 1939.

An incident, the scarcity of hospital beds, was instrumental in prompting Nižetić to perform dacryocystorhinostomy in two steps. Instead of making merely a simple incision into a phlegmonous abscess of the tear sac, the author made the incision where it is done in dacryocystorhinostomy for extirpation of the tear sac, that is, 1 cm. above and 1 cm. below the internal ligament and 0.5 cm. from the internal angle of the lid, curving it slightly toward the temporal side. The ligament was separated cautiously up to its insertion and was incised as far as the crista for a distance of 1 cm. In this manner the lateral side of the tear sac remained untouched. The tear sac, then, was split from the medial side toward the crista instead of from above, and after the pus was allowed to escape it was flushed and packed with gauze strips soaked in an acridine dye derivative (α-ethoxy-6,9-diaminoacridinium hydrochloride; rivanol). The second step of the operation followed after the inflammatory process and discharge of pus had stopped. It consisted in opening the bone and suturing the walls of the tear sac to the mucous lining of the nose. Examination of the permeability of the lacrimal canal is essential in each case. The incision was made through existing fistulas. The result gained by this method was satisfactory, as evidenced in tables in which details are given. The method of Ohm-Dupuy-Dutemps-Bourguet was practiced, except in 1 case in which Toti's method was used.

K. L. STOLL.

Methods of Examination

THE LIMITS OF TYNDALLIMETRY IN THE ANTERIOR CHAMBER. P. C. KRONFELD, Am. J. Ophth. **24:** 51 (Jan.) 1941.

Kronfeld gives the following summary of his findings:

"1. While under ideal conditions slitlamp illumination brings out a very faint Tyndall cone or beam in the normal aqueous humor, under less favorable conditions protein contents of the aqueous up to 10 times of normal may not manifest themselves as a definite beam.

"2. The colloidometer of Roenne, an accessory to the slitlamp, permits estimation of the intensity of the Tyndall cone in the aqueous by comparing it with the Tyndall cone of the lower four fifths of the corneal section, the intensity of which is reduced by means of neutral gray filters.

"3. There is, on the whole, fair parallelism between colloidometric readings and the respective protein contents of the aqueous.

"4. The colloidometer is of definite value for the detection of faint beams under unfavorable optical conditions.

"5. The colloidometric standard, the Tyndall cone of the corneal section, is not absolutely constant. A method is devised by which, again with the aid of the colloidometer, the Tyndall cone of the cornea can be measured and standardized."

W. S. REESE.

Neurology

CONJUNCTIVAL LESIONS IN TUBEROUS SCLEROSIS. T. H. LUO, Am. J. Ophth. **23:** 1029 (Sept.) 1940.

Luo defines tuberous sclerosis as a congenital anomaly often hereditary or familial and characterized by mental deficiency, epilepsy and tumors in various parts of the body. He discusses this condition and its ophthalmoscopic manifestations but remarks that in the literature no cases were found in which there were conjunctival lesions. He gives the following summary of his case.

"In a Chinese female patient with tuberous sclerosis the conjunctiva of the eyelids showed a few small grayish-white, slightly pedunculated tumors. One of the tumors was removed and was found on histological examination to consist of hyperplasia of collagenous fibrous tissue without elastic fibers. In addition to the conjunctival lesions the patient had a white patch in the left retina, which was believed to be a phakoma."

W. S. REESE.

THE EYEGROUNDS OF PATIENTS WITH FUNCTIONAL PSYCHOSES GIVEN INSULIN-SHOCK THERAPY. A. GRALNICK, Am. J. Ophth. **24:** 26 (Jan.) 1941.

Gralnick reviews the literature and then describes the technic and results of his present study. He draws the following conclusions:

"In an ophthalmoscopic study of the eyegrounds of 70 patients with functional psychosis who received insulin-shock therapy, no typical changes were found that could be attributed to the treatment. Retinal detachment occurred in none of the cases.

"There does not seem to be a characteristic appearance of fundi of patients with functional psychosis.

"The duration of a functional psychosis does not influence the appearance of the fundus."

W. S. REESE.

Orbit, Eyeball and Accessory Sinuses

TRAUMATIC ARTERIOVENOUS ANEURYSM OF THE CAVERNOUS SINUS. E. KALT and HÉRAN, Bull. Soc. d'opht. de Paris **51:** 170 (March) 1939.

While riding a bicycle, a girl of 10 years bumped her head against a wall, fracturing the left superciliary arcade without displacing the lower jaw. One month later there was hyperemia of the conjunctiva. Eight months later reducible exophthalmos of 4 mm. was noted. The motion of the eyeball was limited downward. A varix was found at the superior internal angle of the orbit, a thrill was demonstrated by touch. A distinct murmur was heard with the stethoscope. The fundus and the visual acuity were normal. Arterial retinal tension was reduced 35/20. The roentgenogram showed detachment of the quadrilateral plate of the sphenoid bone. It was remarkable that the optic nerve was spared. Treatment consisted of subcutaneous injections of a 2 per cent solution of gelatin up to 50 cc. For permanent cure, the authors believe that ligation of the carotid artery will be necessary.

L. L. MAYER.

Pharmacology

THE DISTRIBUTION OF SULFAPYRIDINE BETWEEN BLOOD, AQUEOUS HUMOR AND CORNEA. K. MEYER, H. S. BLOCH and W. P. CHAMBERLAIN, Am. J. Ophth. **24:** 60 (Jan.) 1941.

Meyer, Bloch and Chamberlain present the following conclusions from their experiments:

"A study of the distribution of sulfapyridine [2-(paraaminobenzene-sulfonamido)-pyridine] between blood, aqueous humor, and cornea of experimental rabbits revealed that after 7 hours the cornea attains a drug concentration equal to or higher than that attained by the blood.

"*In vitro* experiments demonstrated that whole or ground up cornea concentrated the drug by adsorption. In similar experiments with sulfanilamide the cornea attains a drug concentration 3.5 to 4 times greater than that of the buffer solution in which it was suspended. Sulfapyridine was concentrated only 1.4 times."

W. S. REESE.

Physiology

TORSION ASSOCIATED WITH ELEVATION, DEPRESSION AND NEAR VISION. R. CAROW, Arch. f. Ophth. **140:** 86, 1939.

With the cyclophorometer of Harms, the angle subtended by the retinal meridians which convey the subjective sensation of verticality was determined on 107 persons. The cyclophorometer used in these

experiments was a stereoscope or haploscope through which one eye looked at a vertical sheet of graph paper with horizontal and vertical green lines, whereas the other eye viewed the red diameter of a rotary cardboard disk. The latter, as well as the sheet of graph paper, carried in their center black circles which were fused by the examiner. Thereby the position of the eyes was fixed in horizontal and in vertical but not in torsional direction. The examinee was asked to turn the rotary disk until the red diameter coincided with a vertical green line of the graph paper. The angle which the red diameter actually subtended with the vertical lines on the graph paper was the angle subtended by the primarily vertical retinal meridians of the two eyes plus or minus any sensory revaluation that might have taken place during the experiment. These measurements were made under conditions of distance (parallel visual axes) as well as of near vision (convergence of 17 degrees), with the eyes 20 degrees elevated in the horizontal plane and 20 degrees depressed. During distance vision with the eyes in the horizontal plane there usually is a state of disclination which increases on depression. The change from distance to near vision always entails an increase in disclination. All these torsions represent deviations from Listing's law. They serve no useful purpose and, in the author's opinion, probably represent anatomic or innervational peculiarities on the order of heterophorias.

P. C. KRONFELD.

Refraction and Accommodation

TEN YEARS' EXPERIENCE WITH THE COBALT LAMP IN SUBJECTIVE TESTING OF REFRACTION: SPONTANEOUS CHANGES IN ASTIGMATISM. F. RÖSSLER, Klin. Monatsbl. f. Augenh. **102:** 176 (Feb.) 1939.

Rössler reported in 1927 the results of his first experiments on refraction by the help of dispersion of color. Matters have been facilitated by the advent of Zeiss's cobalt lamp, devised by Hartinger. The author examined 10,000 patients with this instrument. He describes the optical and mathematical phenomena, discusses the merits of the cobalt lamp for refraction and outlines his method of examination. The cobalt lamp allows refraction in the presence of lenticular opacities, permitting even conclusions as to whether or not the retina is still normal behind a cloudy lens. Rössler describes the data on 2 youths aged 13 and 20, respectively, in whom accommodation was elimated during his "chromatic" method. Changes of the axis in astigmatism have been observed during examination, as demonstrated by several cases. The possible presence of so-called astigmatic accommodation is discussed in this connection. Sudden changes of the astigmatism were observed in the aphakic eyes of a woman aged 70. Rössler describes the refractive conditions in genuine spasm of accommodation, illustrating this phenomenon by the observation on his own eyes.

Rössler concludes that the eye possesses no rigid refraction; therefore, glasses can never bring about an absolute correction of the refractive error but at best a compromise which reduces the physiologic changes in the eye to a minimum.

K. L. STOLL.

Retina and Optic Nerve

THERAPEUTIC EXPERIMENTS IN CASES OF RETINITIS PIGMENTOSA. I. BIRÓ, Brit. J. Ophth. **23:** 333 (May) 1939.

In the treatment of retinitis pigmentosa Biró succeeded in obtaining more or less improved results with testicular extract in 4 of 5 cases of retinitis pigmentosa, with ovarian extract in 1 of 3 cases, with inhalation of amyl nitrate in 5 of 13 cases and with amyl nitrate combined with liver extract in 2 of 5 cases; that is to say, of 27 cases in which treatment was carried out there was improvement in 13 instances. Patient 27 disappeared prior to the completion of the examination, so that the final results were confined to only 26 patients.

As Biró mentioned several times in other publications in a case of retinitis pigmentosa the type of heredity is of decisive importance as to the condition and function of the eye, and to a certain extent it determines the severe or less severe character of the disease. He stated that according to the observation made at the University Eye Clinic at Budapest retinitis pigmentosa inherited in a dominant manner presents a milder form and can be much more influenced than the form of disease inherited by a recessive route. Attempts to mitigate the symptoms of 35 treated and untreated patients at the clinic failed in every case in which the condition was inherited in a dominant manner. In 9 cases the process of heredity was of a recessive character.

Five patients were the offspring of parents who were blood relations. There were among the patients 6 who were deaf and dumb, 2 who were partially deaf, 2 who were polydactylic and 2 who were suffering from adiposogenital dystrophy. Cortical (posterior) cataract was observed in 11 patients and glaucoma in 1 patient. It was striking how frequent was myopic astigmatism. The Wassermann test was negative in all cases in which treatment was given.

The author stated:

"Surveying the results we see, that besides the unchanged condition, or a very slight improvement of the visual acuity—the slow decline of which can be reduced to a deeper and more central process—the widening of the visual field is more significant. All those substances, with which we experimented, directly or indirectly raised the blood supply of the retina, also its oxidative processes, metabolism, and if only in a slight extent and though transiently, they at any rate restored certain already out-lying areas into normal function of the retina. These cleared up areas, as can be seen in the figures, became displaced chiefly from the equator toward the ora serrata, that is peripherally, further from the equator toward the centre (that is the periphery clears up a little and the concentric constriction widens), which elucidatorily proves the double advance of the gravest degeneration towards the equator, and the possibility of stopping this advance for a short time.

"From the circumstances that with all the above enumerated drugs we succeeded in obtaining improvement of identical character, we may draw the conclusion that neither of these drugs is a specific therapy for retinitis pigmentosa, as the true therapy, the much accentuated tuning of the organism, its endocrine, neurogenic and thus constitutional transformation is yet beyond our knowledge. But by any one of the methods, either the dilating of the arteries or the raising and stimulating of the

metabolism, oxidation, therefore the nutrition of the retina, is capable of improving in some instances and even then to a slight extent. Not so much that it were apt to arouse hopes, but at least in such a measure that it would be a mistake to pass over it indifferently."

W. ZENTMAYER.

DIAGNOSTIC VALUE OF OPHTHALMOSCOPY IN HYPERTENSIVE DISEASES. RISER, COUADAU, PLANQUES and VALDIGUIÉ, Ann. d'ocul. **176:** 254 (April) 1939.

The various branches of the central artery of the retina, the caliber of which is comparable to that of the branches of the arteries which come from the bulbar conjunctiva, are physiologically and histologically the arterioles. Practically terminals, they resolve by progressive histologic transition into capillaries with a unicellular coat of the caliber of a red cell; these capillaries send their branches perpendicularly into the retinal tissue for about 200 microns, as far as the external granular layer. Nonvisible individually, together they gave the appearance of redness to the fundus oculi and a pinkish aspect to the papilla. The veins which come from the capillary network follow a route different from that of the arteries and cross one and sometimes two on their way toward the central vein of the retina. They anastomose with the plexus veins of the choroid.

The authors have studied 140 cases in a complete manner. They list the major changes of the fundus which constitute the principal manifestations of arterial hypertension. 1. The fundamental ocular sign of general arterial hypertension is hypertension in the retinal arterioles, determined by the universally adopted method of Bailliart. 2. The necessity of knowing Fritz's index, which expresses the rigidity of the observed artery, is emphasized. 3. The vascular lesions of the fundus may be seen more clearly. It is not expedient to attribute to certain functional disturbances an importance characteristic of hypertension (black spots, moving objects and flashes of light). 4. Papilloretinitis constitutes another manifestation.

Ophthalmoscopic signs which take precedence in the course of hypertensive diseases are presented. A rigorous physiopathologic and clinical classification of hypertensive diseases appears actually extremely difficult. However, there are a certain number of clinical facts sanctioned by current practice which make certain forms easy to recognize. These forms are: (1) well tolerated arterial hypertension and hypertension with simple arteriosclerosis; (2) malignant arterial hypertension; (3) paroxysmal hypertension, and (4) hypertension associated with diabetes. These four groups are enlarged on in a résumé and in the conclusions.

S. H. MCKEE.

TRAUMATIC RETINAL ANGIOPATHY WITH MACULAR STAR. O. DE CONTI, Ophthalmos **1:** 34, 1939.

A case of traumatic retinal angiopathy of the right eye with formation of a macular star in a 43 year old man is reported. The ophthalmoscopic examination showed a slight blurring of the papilla, moderate venous

engorgement and numerous small white areas along the retinal arteries. A star-shaped edema of the macula was present. The general physical examination revealed moderate arterial hypertension, slight retention of urea and uric acid and traces of albumin in the urine.

After discussing the pathogenesis of Berlin's edema and Purtscher's traumatic angiopathy, the author concludes that the trauma was the determining etiologic factor, while the cardiorenal condition was the predisposing cause of the angiopathy and the macular star.

P. MONTALVÁN.

BILATERAL GUMMA OF THE RETINA. F. MÜGGE, Arch. f. Ophth. **142:** 311, 1940.

In a 27 year old man the ocular disease was preceded by a systemic illness characterized by fever, general malaise, indolent glandular swellings, falling out of hair and recurrent tonsillitis. There had been no gastrointestinal disturbances of any kind and no cutaneous rash. The Wassermann reaction of the serum was found to be positive. Examination of the spinal fluid gave negative results. The patient was treated with mercurials, bismuth and neoarsphenamine. During this treatment the Wassermann reaction became negative, but the subjective visual symptoms, which had been only slight during the first two months of the systemic illness, became more pronounced. Six months after the onset the patient was seen by the author of the paper under review. At that time in each eye one roughly triangular white elevated retinal lesion with a greatest diameter of 6 disk diameters was seen. The retinal vessels appeared severely diseased over the lesions. The Wassermann reaction was negative, but the Kahn reaction was positive. The patient was treated at first with mercurials and large doses of iodides and later with neoarsphenamine. The fundus lesions became smaller and less elevated and broke up into lesions between which the normal choroid shone through. The retinal vessels remained sheathed and irregular in caliber. In the one eye in which the central vision had been reduced to counting of fingers at 2.5 meters there was a return of function to 5/7.5. The ophthalmoscopic appearance and the course of the lesions were similar to those of other fundus lesions reported in the literature as gummas of the retina. The author stresses the fact that the retinal lesions developed in spite of large doses of neoarsphenamine and bismuth preparations but promptly started to regress when the intensive treatment with mercurials and iodides was instituted.

P. C. KRONFELD.

Trachoma

TREATMENT OF TRACHOMA WITH SULFANILAMIDE. W. G. FORSTER, Am. J. Ophth. **23:** 532 (May) 1940.

Forster found that trachoma was arrested in 125 of 167 cases after a three week course of sulfanilamide therapy and in the remainder after a second, similar course. Previous forms of treatment had required two and one-half years to effect an arrest.

W. S. REESE.

How to Realize a Social Rationale and Effective Prophylaxis for Trachoma in Indochina and Especially at Tongking. P. Keller, Arch. d'opht. **2:** 606 (July) 1938.

Keller reviews briefly the status of trachoma from his own point of view. He thinks that trachoma is essentially a disease of infants and a familial disease. He suggests that for an effective prophylaxis the first step is the education of the public and the creation of an anti-trachomatous public opinion in the press, the movies or any other medium of propaganda. The second is the development of prophylaxis in a small community as a demonstration. The third is the extension of the system to a larger and larger area.

S. B. Marlow.

Trachoma as a Labor Hazard. A. Tiscornia and J. M. Vila Ortíz, Arch. de oftal. de Buenos Aires **15:** 105 (March) 1940.

Trachoma is here studied from the viewpoint of its acquisition in industry, with the consequent right of the patient to compensation. The authors hold that workmen should be examined for trachoma on registering to work in any industry, that in the case of any injury to the eyes the prior existence of trachoma should be determined and that persons with trachoma should not be accepted for industrial work.

C. E. Finlay.

Tumors

Pseudomelanomas of the Iris. B. A. Klien, Am. J. Ophth. **24:** 133 (Feb.) 1941.

Klien gives the following summary and conclusions:

"Pseudomelanomas of the anterior surface of the iris may arise through phagocytic activity and proliferation of: (1) the cells of the anterior-border layer of the iris, (2) the adventitia cells of blood vessels near the iris surface, and (3) the endothelium of the cornea whenever it has proliferated onto the anterior surface of the iris.

"All three types of pseudomelanomas are permanent tumefactions of the iris, but their pigment content, which may be either hematogenous or autochthonous, may vary, and it is logical to assume the hematogenous pigmentation to be of a more transient character. Inflammatory conditions apparenty do not play an essential or immediate role in their development; thus they are different from pigmented-organization products of exudate."

W. S. Reese.

Retinoglioma in an Infant of 16 Months. R. Argaud and L. Calmettes, Arch. d'opht. **2:** 593 (July) 1938.

The authors describe a case of retinoglioma and present a detailed histologic study with photomicrographs. They express the opinion that it is useless to be too precise as to the type of cell from which the tumor arises. Their researches show that both granular layers can be the sites of origin of the glial tumor. They think that retinogliomas are embryonic

neoplasms formed by elements arrested in the development of undifferentiated cells and even of spongioblasts, which instead of differentiating into neoblasts and retinal cells remain in a latent condition, a state of heterotrophic inclusion, inactive for a time but not passing the first year of life without the most capricious hyperplasia and metaplasia to form a malignant tumor. They believe that the generic term retinoglioma completed by the indication of the particular characteristic of each variety, for example retinoglioma with rosettes, is the most convenient of all the designations advocated.

S. B. MARLOW.

A CASE OF CYST OF THE ORBIT. C. LABORNE TAVARES and P. ELEJALDE, Ophthalmos **1:** 24, 1939.

A case of bilobular dermoid cyst of the orbit is reported. The extraorbital portion of the tumor had been removed one and a half years previously, but the intraorbital extension had been overlooked at the time. The mass, which was the size of a nut, was situated in the superior and medial portion of the right orbit, displacing the eyeball 4 mm. downward and 3 mm. outward. The cornea was cylindric in the vertical meridian, and there was myopic astigmatism of 12 D. Vision was 20/30. Microscopic examination of the tumor showed a typical dermoid cyst with a moderate amount of connective tissue surrounding the mass. The literature concerning dermoid cysts of the orbit is briefly reviewed.

The article is illustrated.

P. MONTALVÁN.

GLIOMA PRESENTING THE APPEARANCE OF IRIDOCYCLITIS WITH MOVABLE GLOBULAR PRECIPITATES: REPORT OF A CASE. A. VOGT, Klin. Monatsbl. f. Augenh. **104:** 309 (March) 1940.

The author describes and illustrates with slit lamp pictures and photomicrographs the changes in the eye of a girl aged 4½ years with glioma. Numerous round whitish precipitates, resembling the precipitates of cyclitis, were seen on Descemet's membrane, and yellowish dust floated in the aqueous humor. The precipitates were globular, they moved spontaneously and they were deposited in heaps like pebbles. Their diameter was about 0.3 to 0.35 mm. Deposits of these globules resembled tuberculous nodules.

K. L. STOLL.

Uvea

OCULAR REACTION TO FOREIGN PROTEIN: AN ACCOUNT OF A SLIGHTLY UNUSUAL CASE. T. G. WYNEE PARRY, Brit. M. J. **2:** 396 (Aug. 19) 1939.

Cyclitis, with corneal deposits and hazy vitreous, more marked in the right than in the left eye, developed in a young woman in April 1937. The results of the general examination were negative except for a slight reaction to tuberculin. In June the condition became much worse, and the patient was given a course of injections of tuberculin, without improvement in her condition. On October 14 treatment with sulfanilamide was begun, and in November the eyes had entirely healed. The author was loath to ascribe this recovery to sulfanilamide and made a

new survey of her general condition, which was much better because she had stopped eating eggs. She also stated that chicken disagreed with her and that when she slept on a feather bed she never felt rested. On December 16 there was a relapse, which seemed to be due to the patient getting some egg white on the back of her hand while making a cake. A small amount of egg white was rubbed on the patient's left arm to test her sensitivity to it. The skin became reddened and irritable and a definite ocular reaction followed. She was then put on a course of desensitization, and after each injection an ocular reaction occurred.

ARNOLD KNAPP.

A NEW SYNDROME: IRITIS AND ACUTE ULCERS OF THE MOUTH AND OF THE VULVA; ITS RELATION TO RECURRENT IRITIS WITH HYPOPYON. L. WEEKERS and H. REGINSTER, Arch. d'opht. **2**: 697 (Aug.) 1938.

The authors point out that iritis and acute ulcers of the mouth and of the vulva were first observed in 1937, and they give references to the literature. They report a case under observation. They draw attention to the rare condition of recurrent iritis with hypopyon, which is believed to occur exclusively in men. The clinical picture is reviewed. They report a case of this condition in which there were coexisting ulcers of the mouth and of the skin of the genitals similar to those which occur in women. They wonder whether the two conditions are not related. The etiologic factor of these conditions is obscure. Because of the variety of organisms which have been incriminated, the tubercle bacillus most often, the authors suggest that this condition be called recurrent allergic uveitis with hypopyon.

S. B. MARLOW.

Vision

INFLUENCE OF HETEROPHORIAS ON BINOCULAR DEPTH PERCEPTION. H. JUNKER, Arch. f. Ophth. **142**: 366, 1940.

The incidence of heterophorias and their influence on the acuity of binocular depth perception was studied in 500 German sailors whose uncorrected vision was at least 20/20 in each eye and whose hypermetropia determined during cycloplegia did not exceed 1.5 D. in either eye.

Each person was tested with the Maddox rod at a distance of 5 meters and with the phorometer of Stock-Heinsius. In this instrument, which also breaks up fusion by means of a Maddox rod, the fixation target is actually situated a few inches from the eyes of the examinee. The subjective impression of its location in infinity is created by a special optical system interposed between the target and the examinee. The same person tested with both instruments usually showed a slightly higher degree of esophoria (lower degree of exophoria) with the phorometer of Stock-Heinsius. The acuity of binocular depth perception was determined by means of stereoscopic pictures which contained details presenting varying degrees of horizontal disparity (15 to 60 seconds of arc). True orthophoria, that is horizontal, vertical and torsional deviations of less than 1 prism diopter, was present in only 16.5 per

cent of all examinees. The incidence of heterophorias of 1 or more prism diopters is shown in the accompanying table.

By applying statistical methods the author found no relationship between the acuity of binocular depth perception and the presence or absence of heterophoria. In other words, the relative frequency of the lowest and of the highest degree of acuity of depth perception was the same for the orthophoric and for the heterophoric examinees. There

Incidence of Heterophorias of 1 or More Prism Diopters

	Exophoria, Percentage	Esophoria, Percentage	Right Hyperphoria, Percentage	Left Hyperphoria, Percentage	Cyclophoria, Percentage
Maddox rod test	19.0	35.0	6.6	3.4	
Phorometer of Stock-Heinsius	26.8	43.0	6.0	10.6	62.6

was also no demonstrable relationship between the horizontal ductions (the ability to overcome horizontal prisms) and the fineness of depth perception. "Stereopsis seems to be independent of the fusion-free position of the eyes and of the ductions. The ability to perceive lateral disparity and to interpret it in terms of depth appears to be the function of a special cerebral center."

P.C. KRONFELD.

Visual Tracts and Fields

MIDLINE NOTCHING IN THE NORMAL FIELD OF VISION. H. L. BAIR and R. D. HARLEY, Am. J. Ophth. **23:** 183 (Feb.) 1940.

Bair and Harley draw the following conclusions from their perimetric studies:

"Normally a midline notching may be found in the limits of the visual field. Its demonstration requires a coöperative, intelligent subject, steady fixation, and delicate technique. Its explanation, we believe, lies in a thinning of percipient elements in the part of the retina corresponding to the medial border of each half-field. This postulated thinning of percipient elements is based on the conception of each half-field as a unit field because of its separate cortical representation. Being a unit field, its retinal counterpart would have a thinning of percipient elements along all of its borders. Along the macular border the thinning is so slight in proportion to the normal density of rods and cones that its effect is inappreciable."

W. S. REESE.

ALTERATIONS IN ANGIOSCOTOMAS FOLLOWING THE ORAL ADMINISTRATION OF BENZEDRINE SULPHATE. C. M. ROSENTHAL and C. P. SEITZ, Am. J. Ophth. **23:** 545 (May) 1940.

After describing the technic of angioscotometry and the methods used in their investigation the authors give the following conclusions:

"The results of this experiment seem to indicate that Benzedrine sulphate [amphetamine sulfate] administered in quantities (10 mg.) insufficient to bring about marked vascular (blood pressure) and subjective changes does, nevertheless, change the relative blind areas of

the eye. It was also found that the action time of the drug was approximately 30 minutes with the maximum effect at about one hour, the entire effect lasting over a period of three hours." W. S. REESE.

Therapeutics

LOCAL AUTOHEMOTHERAPY IN DISEASES OF THE CORNEA. N. BLUMENFIELD, Vestnik oftal. **18:** 373, 1941.

Autohemotherapy was employed in 24 cases of trachomatous pannus, serpent ulcer, herpetic ulcer of the cornea, etc. The blood withdrawn from the vein was injected immediately subconjunctivally (0.2 to 0.3 cc.) twice a week. Local hemotherapy with conserved blood was tried in 5 cases and a combination of intravenous injection of defibrinated blood from the patient and subconjunctival injection of conserved blood in 12. The conclusions arrived at were as follows:

1. Subconjunctival injection of blood acts more favorably on corneal ulcers than parenteral injection of blood.

2. Local autohemotherapy is preferable to subconjunctival injection of conserved blood.

3. Local autohemotherapy improves the subjective symptoms and causes quick epithelization of ulcers and obliteration of pannus blood vessels; it also shortens the duration of serpent ulcer.

4. The conjunctiva is not improved by local autohemotherapy.

5. No exacerbation of the process in connection with this method of treatment was observed.

6. Small scars were observed between the sclera and the conjunctiva at the site of the injection.

7. In the treatment of traumatic ulcer of the cornea local hemotherapy gave no positive results. O. SITCHEVSKA.

Society Transactions

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Certain Phases in Development of the Vitreous. DR. HENRY C. HADEN, Houston, Texas.

For descriptive purposes the development of the vitreous may be divided into three stages: (1) primary vitreous, composed of a mixture of mesoderm and ectoderm, mesoderm being derived from tissue accompanying the hyaloid artery and the ectoderm from the inner wall of the optic cup and the lens; (2) secondary vitreous, ectodermal tissue which grows from the inner wall of the optic cup (secondary vitreous is the permanent vitreous), and (3) tertiary vitreous, composed of coarser ectodermal fibrils which grow from the part of the inner wall of the cup which ultimately becomes the ciliary region (it develops into the suspensory ligament of the lens). The anterior hyaloid membrane is not a true membrane but is a condensation of the anterior portion of the vitreous. There is no posterior hyaloid membrane. There is no membrane between the vitreous and the retina other than the internal limiting membrane of the retina.

DISCUSSION

DR. F. H. VERHOEFF, Boston: Dr. Haden has given a beautiful photographic demonstration of the generally accepted theories regarding the embryonic formation of the vitreous. I agree with practically everything he said in this regard. However, there is one statement with which I do not agree. He asserted that there is an internal limiting membrane of the retina but not a posterior hyaloid membrane. There are many who agree with him on this point. I believe that there is definitely a posterior hyaloid membrane, but there is a doubt as to whether one should speak of an internal limiting membrane. Sections of an adult human eye stained in Mallory's connective tissue stain show a definite hyaloid membrane stained blue in contrast to the contiguous part of the retina, which is stained red. One of the embryonic specimens similarly stained which Dr. Haden presented on the screen showed such a membrane. When there is a subhyaloid hemorrhage it occurs beneath this membrane, and when the vitreous separates from the retina this membrane comes off with it. If it is not a membrane, then what should it be called? The fact that it is a condensation of the vitreous does not prevent it from being a membrane. I shall not discuss the question of artefacts—any objections along this line would weigh equally against the two of us, since we employed fixed tissues in our studies.

Dr. E. V. L. Brown, Chicago: Dr. Haden's specimens show definitely that the primary vitreous develops in part from the lens, and so far as I know this has not heretofore been demonstrated.

Dr. Theodore L. Terry, Boston: The position which Dr. Haden has taken with regard to the development of zonular fibers from the tertiary vitreous is interesting in its relation to an understanding of involvement of zonular fibers in exfoliation of the lens capsule. If his contention is correct—and there are many observers who do agree with it fully—then the zonular fibers are of a type of material entirely different from that of the lens capsule, and one would not expect the zonular fibers to exfoliate as actively as the anterior capsule of the lens does. If that is the case, then the small particles of exfoliated material often seen enmeshed in the zonular fibers must not have originated there.

The problems related to the development and fate of the blood vessels of prenatal vitreous are extremely interesting. Perhaps considerable information—and doubtless some misinformation—may be gained from study of embryonic specimens of various animals. For instance, only in the rat and in rodents as a class does the vasa hyaloidea propria approach close to the retina to form the membrana vasculosa, which persists as a preretinal vascular layer, the retina itself remaining avascular. In man, on the other hand, the vasa hyaloidea propria does not extend near to the retina. An understanding of the vessel-attracting property in the rodent retina and the vessel-repelling property in the retina of man would probably be of great value.

Blood vessels of the prenatal vitreous are of further clinical interest because of the occasional discovery after birth of persistence of the tunica vasculosa lentis or even of persistence of the vascular system of the primary vitreous in toto. One of the lantern slides showed just such a vascularized mass behind the lens. Dr. Haden had studied the section, which was from an eye removed from an infant nine days after birth because of a clinical diagnosis of retinoblastoma. The connective tissue elements appeared to be mesenchyma in which collagenous fibers were developing. The mass was of larger size than is ever attained by the tunica vasculosa lentis and perhaps even by the primary vitreous itself. It was attached firmly to the ciliary processes and even to the retina. It could not be removed surgically without removal of the tips of the ciliary processes and a part of the retina as well.

The other slides showed similar but less extensive collagenous mesenchyma, containing blood vessels, just behind the lens, and this membrane was also intimately attached to the ciliary processes and to the retina, which is normally very far forward because of the narrow pars plana of the ciliary body at the stage of development pictured. This condition may be concealed by secondary cataractous changes. In 1 instance the lens was largely eradicated by discission. During the second discission the dense membrane could not be cut by the knife-needle. A so-called cataract extraction was performed, and the mass was removed. The surgeon did not realize the real nature of the condition until microscopic study of sections of the material removed showed the presence of typical mesenchyma containing much collagen and many blood vessels. Attached to the mass were several small bits of ciliary body and retina.

The final slide showed the appearance of a bilateral vascularized membrane behind the lenses of an infant born prematurely and weighing only about 2 pounds (907 Gm.) at birth. Dr. Paul Chandler had a similar case and Dr. Charles Perera, of New York, had 3 such cases, in all of which the infant weighed less than 3 pounds (1,307 Gm.) at birth. Is there any reason why prematurity should give rise to a persistence of such embryonic structures, or are they rare and coincidental occurrences?

DR. J. S. FRIEDENWALD, Baltimore: I must disagree with Dr. Haden as to the question of the hyaloid membrane. A number of years ago I devised a technic by which the retina can be stained post mortem and examined on the flat without sectioning. This technic consists of introducing the histologic stains only on the anterior surface of the retina and allowing them to penetrate only through the anterior layers, so that the deeper nuclear layers do not become deeply stained; the retina is sufficiently transparent so that one can examine it well histologically through the anterior surface with high power. Dr. Maumenee, who was at that time working in my laboratory, made some studies with this technic and discovered that on the surface of the retina there is a layer of cells with which he had not previously been familiar. If one examines a preparation of this kind, one sees the ganglion cells of the retina in a regular pattern under the retinal surface and anterior to these cells a layer of cells with elongated nuclei which are distributed in a fairly regular pattern over the surface. These cells, once they are recognized, can also occasionally be seen in ordinary histologic sections, where one sees cross sections of them as exceedingly flat, endothelium-like cells lying anterior to the internal hyaloid membrane. Dr. Maumenee never published this observation, because he found that the cells had been described fifty years ago by His and were known to Parsons forty years ago.

DR. HENRY C. HADEN, Houston, Texas: Naturally, I hesitate to differ in any way from Dr. Verhoeff, because his knowledge of such things is so much greater than mine, but I cannot change my opinion. Slide 9 showed a high power photomicrograph of the specimen Dr. Verhoeff spoke about. One seeing the section under the microscope would have no doubt. There is no question but that the fibers are Müller fibers and that connected with the Müller fibers is what is known as the internal limiting membrane of the retina; moreover, there is no doubt about the fact that the ectodermal vitreous is growing from it. Slide 10 showed the same section farther back in the eye and the same line (internal limiting membrane). It is just an academic question probably whether the internal limiting membrane of the retina is the hyaloid membrane or whether the hyaloid membrane is the internal limiting membrane, but I do not believe that there is any membrane between the vitreous and the retina other than the internal limiting membrane. That which Dr. Verhoeff pointed to in slide 8 is a portion of the vitreous torn loose and colored blue; when seen under the microscope it shows the internal limiting membrane attached to it. At least that is my interpretation of it.

In regard to Dr. Brown's question as to the origin of the ectodermal vitreous from the lens: When the optic vesicle branches off from the

anterior cerebral vesicle it comes into contact with the surface ectoderm. After a time the optic vesicle invaginates, leaving the surface ectoderm. As it turns in to form the optic cup it brings with it fibrils from the surface ectoderm. This part of the surface ectoderm invaginates and forms the lens cup, so that there is a continuation of ectodermal fibrils from its posterior surface to the anterior surface of the inner layer of the optic cup. These fibrils continue to grow after the lens vesicle is formed; they remain in continuity with those of the anterior surface of the inner layer of the optic cup and help to form the ectodermal vitreous.

I am much obliged to Dr. Friedenwald for his discussion and hope that some time he will let me see his slides.

In answer to Dr. Terry, I do not know anything about the blood supply of the rat.

Slide 11 showed that the hyaloid canal is not a canal but is simply the primary vitreous. This has mesodermal tissue in it, which sometimes is not absorbed and goes on to the formation of a connective tissue mass back of the lens. I believe that this process accounts for the appearance in Dr. Terry's slide of a mass in the vitreous behind the lens.

Pigmentary Degeneration of the Retina: Role of the Melanophore Hormone of the Pituitary Gland in Pigmentary Degeneration of the Retina. Dr. P. Robb McDonald (by invitation) and Dr. Francis Heed Adler, Philadelphia.

This article was published in full in the February issue of the Archives, page 264.

Lesions in the Lens Caused by Purulent Corneal Ulcers. Dr. Bernard Samuels, New York.

This article was published in full in the February issue of the Archives, page 345.

Alterations in the Capsular Epithelium in Immature Cataract. Dr. C. A. Clapp, Baltimore.

The author studied lenses removed in their capsules and found certain changes which are of interest. Changes in the capsular epithelium as a result of age have been reported, and these changes have been confirmed.

Three main changes were found: first and most frequent, marked migration of the nuclei of the cells to a considerable depth into the cortical substance; second, almost complete degeneration and absence of the cells and their nuclei, and, third, a proliferation of some of the cells somewhat resembling the proliferation seen in regeneration after injury.

DISCUSSION

Dr. J. Wilkinson Jervey, Greenville, S. C.: I believe, with the essayists, that it is often interesting to speculate on the causes of cataract, but I must say that in the course of more than forty years' practice I have never had the good fortune, or perhaps the bad fortune, to see a cataract that could possibly be explained as the result of a nonperforating

corneal ulcer. A perforating ulcer, or an ulcer which has caused uveitis, brings about a secondary cataract, of course, but I find it impossible to explain to my own satisfaction how a nonperforating ulcer could cause changes in the lens structure. In the first place, such an ulcerative process would have to pass through the very delicate Descemet membrane; how this could take place without leaving a mark on that membrane is beyond my comprehension. Furthermore, I believe, and I have no doubt ophthalmologists all believe, that the predisposing cause of cataracts is nutritional deficiency. One can assume that the changes are due to a lack of balance in the blood plasma of calcium and phosphorus, and it is not difficult to discover physical signs showing, almost without chemical analysis, whether or not there is an imbalance of the calcium-phosphorus content of the blood. Perhaps thirty-five years ago, in my youth and enthusiasm, I evolved a theory that, as is known, slight friction on the surface of the lens would hasten the formation of a cataract. The old massage method of Foster to hasten cataracts was after preliminary iridectomy to use a spatula and gently stroke the surface of the lens. When one encounters a cataract in a person of advanced age one sees a natural, constant, steady source of friction in the arteriosclerotic iris, which is constantly undergoing physiologic hippus, and to my mind most cataracts can be attributed to that source combined with dietary deficiencies. Whether or not this theory seems plausible, I still believe it.

Dr. J. S. Friedenwald, Baltimore: Dr. Clapp spoke of the relation to cataracts of the change in the permeability of the lens capsule. Since I was the first, I believe, to suggest that a decrease in the permeability of the lens capsule might be a cause of senile cataract, I should like to take this opportunity to state what seems to me to be the present status of this theory. At the time I suggested it I was able to show that the capsule of the lens does decrease in permeability with age, and this observation has since been confirmed by several other workers. The hypothesis offered is, therefore, a tenable one, but no conclusive proof has been advanced, and the most one can say is that no one has as yet been able to disprove it. It seems to me that perhaps the statement of the problem in these terms on my part was somewhat naive. There are many factors in addition to a change in the permeability of the capsule which can mechanically interfere with the nutrition of the lens. It is well known that there is an increase in the fibrous tissue of the ciliary processes with age, and hence a barrier exists in the ciliary processes to the diffusion of metabolites from the ciliary capillaries into the posterior chamber, which barrier decreases in its permeability with age. Hence, if senile cataracts are to be attributed to a decrease in the nutritional supply and in the removal of the waste products of the lens, which is still a tenable hypothesis, there are at least two anatomic points where such interference may develop as age progresses.

Dr. Theodore L. Terry, Boston: Dr. Helen S. Mitchell, of Massachusetts State College, has been able with some degree of frequency to produce cataractous changes in rats fed on a heavy galactose diet. I have had an opportunity to study some of the microscopic sections from these animals, and it is interesting to observe what happens to the lens fibers near the equator in the region of the vortex of the nuclear bow. The lens fibers containing nuclei are decidedly increased in number, the increase being somewhat similar to the changes mentioned by Dr. Clapp.

I believe that a discussion of disturbances of the lens epithelium would not be complete unless mention was made of the strong tendency one sees at times for the anterior capsular epithelium to extend all the way around the lens. In speaking of the anterior capsular epithelium, one generally considers that there is no posterior capsular epithelium, but actually the lens fibers themselves make up what would correspond to the posterior capsular epithelium. The first lantern slide depicted the transformation from anterior capsular epithelium to lens fibers in the region of the nuclear bow and the extension of cells of the type of those of the anterior capsular epithelium over the posterior surface to surround the lens. This process is observed in certain mature cataracts and in association with so-called tunica vasculosa lentis. It is interesting to conjecture as to the method by which the condition develops. That the lens fibers of the nuclear bow region lose their ability to lengthen and that, the nuclear bow fibers having died out, the cells of the anterior capsular epithelium, devoid of any obstruction, spread, preserving more or less well their size and shape, appear to be two alternatives. It is hoped that Dr. Clapp has some explanation for this development.

Dr. C. A. Clapp, Baltimore: In reply to Dr. Jervey, I desire to say that I agree with him that the question is largely one of nutrition, but I believe that some form of barrier is a more important factor than the diet of the individual patient. An illustration is seen in the marked increase in the calcium content of the lens in the formation of cataract. The same point has been brought out by Dr. Adler in his work on the various concentrations of urea in the aqueous and the blood stream. Dr. Jervey's suggestion that massage of the anterior capsule alters the nutrition of the lens fits in with my theory that the capsular epithelium plays a role, since it has been shown that massage of this kind causes atrophy of the capsular epithelium.

In regard to the question of the permeability of the capsule, which was brought up by Dr. Friedenwald, I should like to call attention to the difference between the filtration of the clear capsule placed over a glass tube and that of the capsule lined with the capsular epithelium, as found in the living eye.

Operative Treatment of Congenital Subluxation of the Lens. Dr. Arnold Knapp, New York.

This article was published in full in the January issue of the Archives, page 158.

Retinal Periphlebitis in the Course of Acute Exudative Choroiditis. Dr. Arnold Knapp, New York.

This article was published in full in the November 1941 issue of the Archives, page 750.

Wound Rupture After Cataract Extraction. Dr. Harry S. Gradle and Dr. H. Saul Sugar (by invitation), Chicago.

A compressometer was devised to measure the extent to which the eyeball can be forced backward within the orbit and the amount of pressure necessary to produce such motion.

In a series of cases, immediately previous to cataract extraction measurements were made of the compressibility of the eye within the orbit and of the amount of protrusion of the eyeball beyond the anterior plane of the orbit. The frequency of wound rupture was noted.

It was considered that the orbicularis oculi muscle could best be paralyzed for a period of six or seven days by a tenotomy; after seven days, the danger of wound rupture has practically passed.

In a similar series of cases in which measurements of exophthalmos and of compressibility were made, the cataract extraction was preceded by tenotomy of the orbicularis oculi muscle. The frequency of wound rupture in this series was noted.

It is believed that rupture of the wound after cataract extraction is due to increased intraocular pressure brought about by forcible contracture of the palpebral portion of the orbicularis oculi muscle. Such contracture can be eliminated for six or seven days by tenotomy of the muscle immediately prior to the extraction.

DISCUSSION

DR. DERRICK VAIL, Cincinnati: If Dr. Gradle's work holds, I think he has made a splendid contribution to cataract surgery, because the problem of hyphemia after cataract operations is certainly a real one. He mentioned that there are no factors except the external ones that are capable of producing increased intraocular pressure after cataract operations. I must disagree with this statement because, from a clinical point of view, I believe that there is always, or at least in most cases, an increase in intraocular tension; I mean that after the operation the tension decreases and then the anterior chamber overfills and finally becomes settled to the proper, normal state.

DR. W. B. LANCASTER, Boston: So far as I know, this is the first paper read before this society, perhaps in this country, in which definite recognition has been taken of the effect of the external ocular muscles as a factor in wound rupture after cataract. Most writers are content in the belief that the orbicularis muscle alone accounts for what occurs when the patient squeezes. I have never made this point the subject of a paper, but I have stated many times, in papers and in discussions, that in my opinion the external ocular muscles—the rectus muscles at least—are an important factor in increasing the intraocular tension caused by squeezing. In a conversation with Duke-Elder I raised the question, and he stated that he was quite sure that the external ocular muscles are important. He had made experiments on intraocular pressure, using curare completely to paralyze the external ocular muscles. I think ophthalmologists will all agree that the orbicularis muscle is a factor, and if the eyeballs are prominent the orbicularis muscle has a greater mechanical chance. If one fills the orbit with procaine hydrochloride one puts the muscles on the stretch, and it is known that this may increase the intraocular pressure before one begins to operate.

I have been annoyed a great deal with hyphemia and other complications caused by the breaking open of the wound, and my first measures to overcome these difficulties were directed toward protecting the eye from damage by the patient. At one time I put a bandage of water glass all over the head. In hot weather this was uncomfortable,

but it did prevent trauma. However, later I found that even a pasteboard cover, well applied, could furnish satisfactory protection against trauma. For protecting the eyes from the action of the external ocular muscles injections of procaine hydrochloride can be given; these will paralyze the muscles temporarily. In cases of serious involvement some writers have advocated tenotomizing all four muscles before operation. Perfect anesthesia (basic and local) is the best safeguard against injury.

I should like to call attention to an observation that can be made while one is taking the intraocular tension with the tonometer. As a rule the patient flinches as soon as he sees the instrument approaching, and he squeezes. One can hold the lids open, and if one looks carefully one will see the eyeball retract perceptibly into the orbit, owing to the contraction of the extraocular muscles, and I believe it will be admitted that the contraction of these muscles will raise the intraocular pressure. I recently demonstrated that it will. I measured the tension with the patient squeezing slightly. It was over 30, and I did not think it would be so high, since the patient had been under treatment for a long time and was responding well. I instilled another drop of the anesthetic and spoke to him a while; then I again took the tension and found that it was 20. This is definite proof of the effect of squeezing, not by the orbicularis muscle, which is held away from the eyeball, but by the external ocular muscles. The point I wish to bring out, therefore, is that there are two factors—the orbicularis and the external ocular muscles. It is not enough simply to control the orbicularis muscle, whether by injection or tenotomy or with the speculum, because during operation squeezing is a reflex from some sensation which should be prevented. During convalescence the best safeguards are: (1) to keep the patient comfortable—not flat on the back; (2) to use sedatives judiciously, and (3) to apply good, perfectly appositional, scleral sutures, at least two and often three.

Dr. F. H. Verhoeff, Boston: Dr. Gradle has stated that wound rupture after a cataract operation is caused by increased intraocular pressure resulting from contraction of the orbicularis muscle. He has described an experiment made by him, which he regarded as proof that forcible closure of the lids may increase the intraocular pressure sufficiently to rupture the wound. It seems to me that this experiment was unnecessary, since it is obvious that closure of the lids could increase the intraocular pressure sufficiently to rupture a recent wound provided the pressure was unapposed by pressure from without. Apparently Dr. Gradle has overlooked the fact that at the same time the lid pressure raises the extraocular pressure to an equal degree. His experiment, therefore, throws no light on the question of to what extent lid pressure in the absence of a speculum tends to rupture the wound. Experiments of a different kind would be necessary to provide an answer to this question. If the extraocular pressure was not raised by lid pressure, wound rupture would no doubt occur after all cataract operations.

To me wound rupture after cataract operation presents no serious problem. Two sutures properly inserted prevent rupture such as that to which Dr. Gradle refers. Of course sutures will not prevent rupture of the wound in cases of exceptionally severe trauma. For example, one of my patients was struck in the eye by a fist during a fight. The blow

resulted in rupture of the wound, prolapse of the iris and serious intraocular hemorrhage. Except for such severe trauma, the only cases in which I have had prolapse of the iris have been a few in which there was loss of vitreous at the operation. The insertion of three or four sutures would no doubt have provided protection in these cases. Such prolapses are so infrequent, however, that I have used only two sutures.

Dr. Arnold Knapp, New York: Colonel Smith always insisted on the danger of having a patient turn down his eyes during a cataract operation. He frequently spoke of a twisting movement of the eyeball which generally preceded escape of vitreous in the intracapsular operation, and this bears out the point which Dr. Lancaster made, that it is the oblique muscles in particular that are a factor in opening up the wound. However, I agree with Dr. Gradle that the orbicularis is an important muscle, particularly in cases in which the eyeball is prominent. The prominent eyeball is the one likely to give the operator trouble.

The question of the importance of sutures has naturally been raised. I cannot say that in my experience the insertion of sutures has prevented the occurrence of hyphemia or rupture of the incision.

Finally, I have the impression that the opening of the wound occurs on an average in the early morning of the fifth day, and I ascribe its occurring then to lack of sufficient sedation and inadequate nursing. I believe that the fifth day is about the time that the patient is given the use of one eye, and he becomes more or less careless, not realizing the seriousness of the operation he has had, and as he is still more or less sleepy he inadvertently squeezes his eyes. I should like to ask Dr. Gradle whether any deformity of the lids has resulted from the procedure he described.

Dr. J. S. Friedenwald, Baltimore: I should like to raise two questions. I am interested in the instrument which Dr. Gradle has devised, not, however, for the purpose for which he has devised it, but for the possible study of the mechanism of exophthalmos in cases of orbital tumor and hyperthyroidism, and I hope that he will make the instrument available to the medical profession for study in such cases.

I should like to ask just what the anatomic basis is for making two incisions close together in the orbicularis muscle near the external canthus and why the two are more effective than a single incision straight out from the canthus.

Dr. Harry S. Gradle, Chicago: Although I acknowledge that the extraocular muscles may play a definite role in increased intraocular pressure when they are brought under tension, I believe that they are of minor importance as compared with the orbicularis muscle. I base this belief on the experiment which Dr. Verhoeff described as needless but which I consider has much merit, namely demonstration of the fact that with the manometer needle in the vitreous chamber one finds a definite pressure but after filling the posterior half of the orbit with 2.5 cc. of procaine hydrochloride one finds no increase in the pressure of the eye until a contraction of the orbicularis muscle occurs. Thus, if the extraocular muscles themselves cause a pull on the eyeball, owing to the proptosis alone, as is readily conceivable, then the pressure in the eye should have been raised before the contraction of the orbicularis muscle took place.

In answer to Dr. Knapp I will say that I have never seen any deformity of the lids result, as the canthotomy wound closes spontaneously and without the aid of sutures. It may be remembered that Axenfeld employed canthotomy in all his cataract operations, but not for this reason. He utilized it in order to obtain more room and to flood the conjunctival sac with fresh blood, to which he attributed many bactericidal powers.

Replying to Dr. Friedenwald, I would say that the orbicularis muscle has definite fibers that originate in the periosteum of the outer canthus, some coming from above and some from below. Consequently a single incision through the orbicularis muscle will not sever the fibers completely. If one refers to the Sobotta-McMurrich atlas one will see that these fibers are so arranged that with one incision it would be impossible to prevent the contraction of the orbicularis muscle from affecting the upper lid and the lower lid simultaneously.

Cataract Extraction with Iridodialysis. Dr. William P. Beetham, Boston.

Cataract extraction through iridodialysis has been adopted by the author as a routine procedure. The cosmetic results are satisfactory. In all except a few of 125 consecutive private cases good results were obtained, and the failures were not necessarily due to the method of operating.

Procedures in Intracapsular Cataract Extraction: A New Method. Dr. Daniel B. Kirby, New York.

In a small percentage of selected cases, ordinary safe rotation and pressure did not effect the desired intracapsular extraction. The superior portion of the zonule was observed not as individual fibers but as an almost transparent lamella through which when the lens was tilted and lifted the vitreous could be seen as a dark body lying relaxed in a normal position. The hyaloid membrane was seen 3 or 4 mm. posterior to the equator of the lens. Traction suture afforded a direct view. Experience proved it safe to touch the equator of the lens with a blunt instrument and see the zonule strip off. A combination of clockwise and counterclockwise rotation and stroking of the equator of the lens may loosen the zonule, which is otherwise resistant, and allow delivery of the cataract in its capsule.

The author has had four years of experience with this new method, having used it in about 20 cases, and believes it is feasible and practical for difficult operations. It is not recommended for teaching or adoption, although the author has had no reason to regret its use.

Results of Cataract Extraction. Dr. Edward Jackson, Denver.

DISCUSSION OF PAPERS BY DRS. BEETHAM, KIRBY AND JACKSON

Dr. George H. Cross, Chester, Pa.: Several years ago, when confronted by the necessity of removing a lens that was dislocated backward in the vitreous, I devised an inexpensive instrument for removing it. This consisted of an ordinary darning needle which, after the temper

was drawn, was bent at an obtuse angle and then curved in a half circle and held in a small pin vise. When this instrument was used the point was engaged in the lens; the handle was then rotated between the fingers, and the lens was drawn up so that it could be looped out.

By using the principle of this instrument but changing the point to a rounded end, flattening the curved portion and making a right and a left, it was possible to insert the needle and with a sliding motion rupture the zonula, so that when the lens was grasped in the intraocular forceps it could be removed without causing trauma. I had previously made an instrument for the same purpose, sliding a sharp point through a curved cannula to rupture the zonula; however, this proved too complicated and its use was discontinued.

Another point I would stress is that of performing a small peripheral iridectomy, which reduces the photophobia and has the advantage of leaving a round pupil. At times the iris was incarcerated even when physostigmine was instilled. So, in addition to the aqueous solution, physostigmine in an ointment base was used; the action of the drug was thus prolonged and the number of cases of incarcerated or prolapsed iris reduced.

DR. WILLIAM P. BEETHAM, Boston: As there is no discussion about iridodialysis, I wish to add a comment about corneoscleral sutures. In spite of the fact that there were 3 or 4 cases of prolapse of the iris which occurred with the use of corneoscleral sutures, I believe that these are the most secure sutures that can be used to close the corneal incision. In 2 cases I had the following experiences:

In the first the eye was lost because of purulent endophthalmitis. The patient was senile and diabetic and culture of material from the eye negative. Operation had been approved by Dr. Joslin, and I considered it safe to operate. I had to scoop the lens, which resulted in a small loss of vitreous; at the end of the operation the eye looked satisfactory, but a few hours later pain developed, and eight hours after the operation I removed the dressing. The cornea was hazy and cloudy; the anterior chamber was hazy, and the vitreous was gray. At this time the pressure was 80 mm. of mercury (Schiøtz). On the following day the pressure was equally high, and on the third day I eviscerated the eye. On culture a peculiar germ resembling the hay bacillus was found.

In the second case, in which there was glaucoma, I had operated by intracapsular extraction without loss of vitreous. The next day the patient complained of discomfort. As a rule I do not dress the eye unless the patient complains of distress. I found that the cornea was hazy. The occurrence took place in a hospital in which I had had trouble with anesthetics being reautoclaved, and I had this fact in mind. On feeling the eye I found that the pressure was increased, and the tension was 55. The administration of pilocarpine was instituted, and the tension has not since been above 20.

I cite these 2 examples to show how high the pressure can go and the corneal sutures still hold.

DR. W. B. LANCASTER, Hanover, N. H.: What does Dr. Beetham put in the eye immediately after operation?

DR. WILLIAM P. BEETHAM, Boston: Physostigmine ointment.

DR. DANIEL B. KIRBY, New York: I wish to thank Dr. Cross for his discussion. Did I understand correctly that the zonula below is ruptured by his maneuver?

DR. GEORGE H. CROSS, Chester, Pa.: Yes.

DR. DANIEL B. KIRBY, New York: I should hesitate to interfere with the zonula above if I could not see directly and exactly what was going on and operate under direct view. Dr. Waite, in Boston, has worked for a number of years on zonulotomy below, and he sent me a letter describing his procedure, which I have seen him perform. When he uses it, it works out well, although he has not published a report of his work.

I do believe in and am using external canthotomy, as Dr. Gradle spoke of it, with the horizontal and the vertical cut through the orbicularis muscle in certain cases. I put in the speculum and use it if I find any evidence of pressure of the ring of the lids on the globe, particularly in the equatorial portion of the eye. I use it for a different purpose than Dr. Gradle does: in certain cases to avoid the loss of vitreous by equatorial pressure.

The point of my direct interference with the zonula above is that the maneuver is another resource in operations for cataract. With only one maneuver to depend on, one would be apt to be disappointed in cases of cataract difficult to manage.

DR. EDWARD JACKSON, Denver: I have only a few words to say but they are appropriate at this time and will reenforce the suggestion expressed in my paper. I have never, even in cases of rupture of the cornea, used the corneal suture. I have too much respect for the cornea to pass a needle through it. One thing, which does not bear especially on the subject under discussion, is this: I have usually avoided postoperative hemorrhage into the eye by operating with the patient in a sitting posture. Many years ago I performed a cataract extraction and after the operation encountered hemorrhage. As I was about to leave the hospital, after having dressed the eye, I was informed that the patient, a comparatively young man, was complaining of pain. I returned to the operating room and found the man still lying there. On examining the dressing, I found on it evidence of oozing of blood. I immediately seized the man by the neck and shoulders (he was still lying on the operating table), threw his feet down and raised him to a sitting posture. I held him there, as I recall it, for from fifteen minutes to possibly half an hour, until all tendency to bleeding from the eye had ceased. He had no subsequent hemorrhage. Since then, particularly when the patient has a large abdomen, where there is an enormous amount of blood in the abdominal vessels, I have operated with the patient in the sitting posture. Under this circumstance I have never seen the operation complicated by expulsive hemorrhage, although some of the patients have presented a distinct history of hemorrhage (one of them had had cerebral hemorrhage, and another had been operated on for glaucoma years before).

Rhabdomyosarcoma of the Orbit. DR. F. PHINIZY CALHOUN JR. (by invitation) Atlanta, Ga., and DR. ALGERNON B. REESE, New York.

The article was published in full in the March issue of the ARCHIVES, page 558.

Survey of Records of Glaucoma in Ophthalmic Clinics. Dr. Mark J. Schoenberg, New York.

This article is published in full in this issue of the Archives, page 716.

Carbaminoylcholine Chloride in the Treatment of Glaucoma Simplex. Dr. C. S. O'Brien and Dr. K. C. Swan (by invitation), Iowa City.

This article was published in full in the February issue of the Archives, page 253.

Cyclodiathermy: An Operation for the Treatment of Glaucoma. Dr. C. H. Albaugh (by invitation), New York, and Dr. Edwin B. Dunphy, Boston.

This article was published in full in the March issue of the Archives, page 543.

Ocular Kinetic Righting Reflexes. Dr. Alexander E. MacDonald, Toronto, Canada.

In 1919 Gordon Holmes, from a study of war wounds, demonstrated the propagation of the retinal nerve fibers to the calcarine area. The physiologic importance of this distribution as the basis for an ocular kinetic righting reflex is advanced, with evidence of dominant quadrants and horizontal and vertical visual raphes. In space perception, in displacement discrimination and in orientation its importance to the static and to the kinetic observer is paramount.

Moore's Subjective "Lightning Streaks." Dr. F. H. Verhoeff, Boston.

Moore's subjective "lightning streaks" are frequently observed by patients with numerous senile opacities of the vitreous. In most cases the streaks are referred to the temporal field, but in the same case they may be referred also to the upper, the lower and the nasal field. The patient probably does not actually know from which eye the streaks arise but guesses correctly because they appear most conspicuous on the same side as the affected eye.

The streaks are dependent on separation of the vitreous. A streak is produced when an ocular movement causes a sudden impact of the shrunken vitreous on the peripheral retina.

The associated apparent increase in opacities of the vitreous is due to the concentration of the previously existing opacities in the smaller space occupied by the shrunken vitreous.

The predominance of the streaks in the temporal field is probably due to the fact that this field extends nearest to the periphery and also to asymmetry of the vitreous body.

The streaks are of slight, if any, prognostic importance.

Treatment of Blepharospasm. Dr. W. L. Benedict, Rochester, Minn.

The treatment of blepharospasm that has given the best results according to published reports has been resection of the branches of the seventh nerve which supply the orbicularis oculi muscle. This operation leaves unsightly scarring of the face and may have to be repeated at intervals of one or two years. At each successive operation more extensive surgical

intervention must be done, and in the end this brings about considerable disfigurement.

Injection of alcohol into the nerves in the region of the parotid plexus gives equally satisfactory results without scarring of the face. The injection usually provides relief for from three months to one year.

DISCUSSION

Dr. Albert N. Lemoine, Kansas City, Mo.: I have been injecting alcohol for blepharospasm since 1933. I do not use the method advocated by Dr. Benedict, but I have injected alcohol into the branches of the facial nerve as advocated by Van Lint in cataract operations. The injection has been found to be efficacious in most cases. I have had patients in whom there was no recurrence for as long as two years. The method is also handy for treating spastic entropion even if the condition is due to irritation of the conjunctiva or of the cornea. In treating spastic entropion I inject alcohol into the lid in the same manner as for blepharospasm; the injection relieves the entropion and the ocular condition clears up much more quickly. I can recommend this method highly, and I believe that in the future I shall make my injections as Dr. Benedict does.

Dr. Alexander E. MacDonald, Toronto, Canada: Some of my most grateful patients, I am sure, are those I have treated for blepharospasm by injecting alcohol, after the method of Van Lint, into the orbicularis muscle opposite the external canthus. Before the alcohol, procaine hydrochloride is used for the relief of the pain, which is considerable.

There is a serious type of blepharospasm due to a lesion of the gasserian ganglion or of the central nervous system or, more often, to hyperirritability of a muscle due to calcium deficiency and ocular strain. Twitching of the orbicularis muscle due to fatigue is well known, and frequently blepharospasm is a reflex condition. Riboflavin deficiency may be associated with the calcium deficiency, and this produces sensitivity to light; so in the early stages these factors should influence treatment and injection should be reserved for severe conditions.

Dr. W. L. Benedict, Rochester, Minn.: I know that Dr. Lemoine has lectured on this subject and has given courses of instruction in it. I believe that most physicians have been satisfied with the treatment, which consists of deep injection about the rim of the orbit. One of the patients on whom I reported had been treated by a neurologic surgeon elsewhere. He injected above the eyebrow for a tic which involved the lower part of the orbicularis oculi muscle. In that case I found that by pressure below the malar bone, the blepharospasm could be controlled. I believe that most ophthalmologists refer such patients to neurologists, but in my opinion ophthalmologists can handle the patients themselves.

In regard to Dr. MacDonald's comments, I would say that I have found no reference to riboflavin insufficiency in connection with this condition.

Papilledema Without Increased Intracranial Pressure. Dr. Arthur J. Bedell, Albany, N. Y.

Six cases of papilledema without demonstrable evidence of involvement of the brain were reported. In 4 the condition was unilateral, and the patients' ages were 13, 18, 28 and 38 years. In 2 the condition was

bilateral, and the patients were 22 and 43 years old. Visual acuity was decidedly reduced.

There was a recurrence of the swelling in the 13 year old patient, and the 22 year old patient had three separate attacks, in which the bilateral swelling became extreme. Complete physical examinations and laboratory tests failed to disclose any gross abnormalities.

DISCUSSION

DR. ALBERT N. LEMOINE, Kansas City, Mo.: I have seen 3 patients with papilledema with apparently no increase in intracranial pressure. The first 2 were seen thirteen years ago. The first patient was a girl aged 12 whose history was essentially noncontributory except to reveal that she had never menstruated. She came to see me six weeks later; the papilledema was gone and the fields and vision were normal, and they have remained so.

The second patient, a woman aged 21, was seen during the same year. She had 4 D. swelling of the optic disks and 25 degrees of bitemporal contraction of the visual fields, with a slight enlargement of the sella turcica. The vision was reduced to 20/30— in each eye. Complete physical and laboratory examinations were made, and all gave negative results. I observed the patient for three months without finding any change in her condition. She married, and came back two months later, having in the meantime become pregnant. The papilledema was gone; the fields were normal; the vision was normal.

The third patient, a girl aged 13, is under my observation at the present time. I saw her first on March 27, 1941. She was totally blind in the right eye, with only light perception in the left eye. She had 4 D. of swelling in the left eye and 5 D. in the right eye. The laboratory examinations and the roentgen examination of the sinuses and the skull gave completely negative results. A neurosurgeon insisted that there must be something to account for the condition, and a spinal puncture was made; the pressure was 13 mm. of mercury. Since we were not satisfied with the results, an encephalogram was made. This also gave negative results. The girl's history was essentially noncontributory except to reveal that she had never menstruated and had had blurred vision for a few weeks before the onset of her blindness, which came on suddenly and was accompaniel by severe pelvic pain. She received no treatment. I saw her on May 27, and her vision at that time was 20/200; the fields were normal, and the swelling was completely gone.

DR. WALTER I. LILLIE, Philadelphia: Apparently there is considerable confusion among ophthalmologists concerning the interpretation of edema of the disk. Dr. Bedell's presentation is in my opinion a classic description of 5 cases of acute optic neuritis. One sees many fundus conditions that exhibit edema of the disk, or papilledema. Such edema occurs in thrombosis of the central retinal vein; in increased intracranial pressure, commonly called choked disk; in the retinitis of angiospastic and malignant hypertension; in the retinitis of nephritis, and in optic neuritis, In a case of precipitous loss of central visual acuity in which the fundus examination shows edema of the disk, the diagnosis so far as I am concerned is optic neuritis. In cases in which there are neurologic symptoms, headaches and the like, in which there is as much edema of the disk as,

or more than, in acute optic neuritis due to increased intracranial pressure, there is no precipitous loss of central visual acuity. Edema of the disk per se does not cause loss of central visual acuity, and when this is lost and lost precipitously, the loss is one of the cardinal signs of inflammation, namely loss of function in that particular tissue at that particular time. Dr. Bedell had no time to give a detailed report of all his cases, but from his description of the fundus changes I would not hesitate to say that each is a case of acute optic neuritis. The process is the same in retrobulbar neuritis and in optic neuritis, but in retrobulbar neuritis the inflammation is behind the globe. The clinical course is similar except that the prognosis is much better in retrobulbar neuritis than optic neuritis because the fibers can readily stand swelling in the optic nerve where there is no compression. But when the inflammation is at the optic disk the nerve fibers are pinched against the lamina cribrosa and are damaged much more rapidly, and the return of good central visual acuity is usually much slower in the case of optic neuritis than it is in the case of retrobulbar neuritis. Permanent visual changes in retrobulbar neuritis generally occur when the optic nerve is involved in the optic canal, as in this circumstance too the inflammation is confined to a small bony canal and destruction of the fibers occurs much more readily. Dr. Bedell has shown excellent photographs of papilledema in cases of precipitously lost central visual acuity. To me this is a typical clinical syndrome of acute optic neuritis, and there should be no associated increased intracranial pressure.

Dr. Ralph O. Rychener, Memphis, Tenn.: It is with some hesitancy that I discuss Dr. Bedell's presentation, as I am not certain that the patient whose optic disks I wish to show has the particular condition under discussion. However, it seems to me that one eye must be classified as having papilledema, whereas the other apparently has true optic neuritis.

Dr. F. H. Verhoeff, Boston: I wish to express my appreciation of Dr. Lillie's discussion. I tried to get recognition before he did, but I am glad that I failed, since he expressed what I had in mind much better than I could have expressed it and brought out some points that I would not have mentioned but in which I concur. However, he failed to mention one important symptom, namely pain. Dr. Bedell and the other speakers also neglected to refer to this. Pain on pressure and on movement is characteristic of acute retrobulbar neuritis. I use this term whether the lesion is immediately behind the globe or farther back, that is to say, whether or not there is edema of the optic disk. I always regard the condition as multiple sclerosis, even if the patient never acquires any other symptom of this disease. I believe that multiple sclerosis can be confined chiefly to the optic nerve.

Dr. H. M. Langdon, Philadelphia: In his interesting talk Dr. Bedell has raised the question of differential diagnosis between papilledema and optic neuritis. In many of his cases—most of them, I believe—there was an abrupt loss of vision. The classic example of papilledema is that which occurs in association with a frank intracranial neoplasm with increased intracranial pressure. The vision does not deteriorate rapidly. In many cases the patient is watched for weeks before there is any decided loss in central vision. The disease in some of Dr. Bedell's

cases lasted only twelve to thirteen days, during which time, I understand, there was a distinct loss of vision and then an abrupt return to normal conditions. He did not, so far as I could gather, describe the visual condition before the attack in his last patient—the one who had a swollen lid and was pregnant. In the other cases it seemed to me that there were a very abrupt loss of vision and an abrupt return of vision. That is not in my opinion consonant with mere papilledema, without actual inflammation of the tissues, but it does fit in perfectly with conditions found in acute ocular diseases.

Dr. Arthur J. Bedell, Albany, N. Y.: Dr. Lillie spoke of the classic signs of inflammation and stressed edema. He also stated that the good end result in retrobulbar neuritis is in marked contrast to the poor result in optic neuritis. He did not assert that papilledema is absent in the cases reported by me.

In answer to Dr. Rychener's question: Patient 6 was thoroughly tested by a competent allergist, who reported that there were no reactions.

Dr. Verhoeff raised an interesting question, one that proved how often anatomy is forgotten. He stated that one of the characteristics of inflammation is pain on motion of the eyeball and tenderness of the globe to touch. That statement is found in textbooks; but surely swelling of the optic nerve as it impinges on the fine nerve fibers which encircle the nerve in the region of the optic foramen may come from pressure from fluid as well as from inflammatory exudate.

Dr. Langdon declared that an abrupt improvement of vision is a sign that the condition was inflammatory. Greater experience will teach him that sudden release of fluid reduces pressure much more rapidly than does the resolution of inflammatory products.

Ring Ulcer of the Cornea. Dr. Sanford R. Gifford, Chicago.

This article was published in full in the February issue of the Archives, page 231.

Ocular Pemphigus and Its Relation to Pemphigus of the Skin and Mucous Membranes. Dr. Alfred Cowan and Dr. Joseph V. Klauder (by invitation), Philadelphia.

Conditions of the eye which are generally known as pemphigus of the conjunctiva and essential shriveling of the conjunctiva are divided into three types: 1. Acute pemphigus of the conjunctiva. This disease in all probability represents a severe variant form of erythema multiforme. 2. Pemphigus of the conjunctiva. This is regarded as one phase of pemphigus of the mucous membranes. Ocular lesions may precede, accompany or follow lesions of other mucous surfaces and/or of the skin. The disease may end fatally through generalized cutaneous pemphigus, or the ocular lesions may be the sole manifestation of the disease. 3. Shriveling of the conjunctiva. This embraces conjunctival lesions simulating, but different from, pemphigus and accompanying a variety of bullous cutaneous diseases.

DISCUSSION

Dr. C. A. Clapp, Baltimore: In 1924 I presented a paper on ocular pemphigus before this society. I reported 6 cases and brought the litera-

ture up to date with 186 reported cases. I have observed 3 or 4 cases since that time. The condition is, I believe, relatively infrequent; Franke reported that it occurred once in 9,000 cases, whereas Posey found it only once in 75,000 cases.

The making of a differential diagnosis is important, as well as the question whether essential shrinking of the conjunctiva and pemphigus are one and the same. In 1924 I expressed the opinion, in which I agreed with von Graefe, that the two conditions are different stages of the same disease, but I am gradually coming to the opinion of the authors of this paper that in all probability each is a separate entity.

A great difficulty in making a differential diagnosis is the lack of any positive laboratory test. Pels and Macht, of Baltimore, found that the blood of patients with pemphigus is toxic to Lupinus albus seedlings, but I do not believe this test is an absolute one.

I wish to ask the authors if they know of any complement fixation test for pemphigus, since it was stated recently (Smith, B.: *Am. J. Ophth.* **24:** 451, 1941) that such a test was being performed in Washington, D. C. I regret that the authors were not able to clear up the causation or to offer some help in the treatment of this condition. In my opinion the diagnosis is comparatively easy, but the present treatment is certainly most unsatisfactory.

Dr. Sanford R. Gifford, Chicago: Dr. Cowan is to be congratulated on having had Dr. Klauder, a dermatologist, to help him in his cases. I have experienced great difficulty in interesting any dermatologist in patients with ocular pemphigus. Some will say that the patient doesn't have pemphigus, and that is all they know about it. If one is fortunate enough to find a dermatologist who will look into the various orifices, as the ophthalmologist does not have the equipment or the opportunity to do, I believe one will learn that such patients have lesions on the mucous membranes. I have observed 2 new cases in the last two months. I have sent blood from a total of 8 patients to Macht, of Baltimore, and the specimens have all shown a high toxic index in the serum.

What I wish to speak about is the effort to correct this condition surgically by the use of mucous membrane grafts. I saw a patient, reported on ten years ago by Dupuy Dutemps, and I attempted to repeat the result; the cornea was just beginning to be involved, and I believed that with the use of extensive mucous membrane grafts I might be able to preserve the viability of the cornea a little longer. I had no difficulty in making the grafts heal, but the process went on to involve them; so the ultimate result was the same. In fact, in 1 case it was precipitated by the operation.

One thing that can be done for the patient is to correct the trichiasis, which is almost always present, by the Van Millingen operation, an intermarginal lip graft being used. This procedure is simple, and trichiasis is one condition that leads to damage of the cornea. In a recent case in which there was a scanty lacrimal secretion, I believed that it was worth while to close the tear points by the Beetham method. The patient obtained great relief. In another case I did just the opposite. The patient had both her canaliculi closed by cicatricial tissue, and the ducts of the lacrimal gland were not involved, so that there was profuse tearing. In this case I employed the procedure of Nizetic and succeeded in restoring the patency of the canaliculi.

DR. DERRICK VAIL, Cincinnati: I wish to express my thanks to Dr. Cowan for clarifying the issue. It is not unusual in a large general hospital to have an occasional case of pemphigus, and my experience with the dermatologic consultants has been an unhappy one, for they all make a diagnosis of erythema multiforme, and that is all.

I should like to place on record a case in which there are most unusual features. The patient was a young woman desperately ill with acute pemphigus involving all the mucous membranes in the body, including probably the gastric mucosa. When I saw her the right eyelids were completely sealed—there was no aperture whatever. The left eye presented the characteristic picture of shark skin membrane and symblepharon. Because of the movement of the right eyeball beneath the lids I considered it worth while to attempt to separate the lid margins. This was done fairly easily. One of the interesting features was the slimy character of the blood. When the lids were opened they disclosed a clear cornea, which in twenty-four hours became hazy. Everything possible, including a contact glass, was tried, and all kinds of oily solutions were used. I even used amniotic fluid as a therapeutic measure in the effort to prevent adhesions from forming. The only thing that helped the patient generally was the repeated transfusion of normal blood. At the present time she is living and fairly well. She has difficulty with her nutrition, and large doses of vitamins are administered parenterally. Both eyes are practically blind and covered with shark skin membrane.

DR. ARTHUR J. BEDELL, Albany, N. Y.: (Two photographs were shown to illustrate pemphigus.) The first photograph shows how the thickened membrane extends over the cornea, but that it can be penetrated by infra-red rays proves Dr. Vail's point that the cornea beneath it is clear.

The second photograph is of a patient seen during several acute exacerbations. It shows the development of the conjunctival fold.

I had hoped to hear more about the acute stages of pemphigus, because occasionally at the onset of the disease distinct bullae appear on the cornea or on the tarsal conjunctiva. These disappear, and new ones form. They increase in number and extent and finally result in cicatricial contractions. The patient pictured had three distinct bullae within several months. Below the cornea there were elevations of the superficial epithelial layer, which are not to be confused with those caused by epithelial dystrophy.

DR. ALFRED COWAN, Philadelphia: In my opinion the condition is more frequent than is generally believed. Of 16,000 blind persons in Pennsylvania, 11 had pemphigus.

In answer to Dr. Clapp I would say that so far as is known there is no laboratory method of diagnosing this disease. The diagnosis must be made clinically.

Dr. Gifford mentioned the use of grafts. In our experience there was no response to treatment of any kind. When grafts are made they may heal up, but the process goes on. Nothing, it seems, will stop it, at least nothing that we know of. Dr. Vail brought this point out well in his case.

What Dr. Bedell says is true, but what he regards as an acute condition is nothing more than an exacerbation of a chronic condition. The disease process is slowly progressive and goes on over a number of years. Every once in a while the patient will have a flare-up, in which there is a redundancy of the tissue, which seems to be in contradistinction to the eventual contraction and decrease in the amount of conjunctival surface. I have examined patients carefully with the slit lamp, and in every case of skinlike membrane the cornea is involved. Although the cornea may be seen in the infra-red photograph, with the aid of the slit lamp it can be seen to be affected.

Cultural Studies on Patients with Uveitis and Other Ocular Diseases.

Dr. Conrad Berens, Dr. Sidney Rothbard (by invitation) and Dr. D. Murray Angevine (by invitation), New York.

The present communication is concerned with cultural and immunologic studies made during the past four years of 142 patients with acute or chronic ocular lesions in an attempt to isolate an etiologic agent. Sixty-three patients had either acute or chronic uveitis, and of 65 with other inflammatory ocular diseases, 28 had chorioretinitis, 16 keratitis, 6 endophthalmitis, 9 conjunctivitis and 5 optic neuritis. Control studies were also made of 14 patients with noninflammatory ocular diseases.

During the period of this investigation, 83 patients with active rheumatoid arthritis and 22 with rheumatic fever were also studied. The results of these findings have been published (*J. A. M. A.* **115:** 2112 [Dec. 14] 1940).

According to numerous investigators, uveitis and rheumatoid arthritis or rheumatic fever occasionally occur in the same person, and because the etiologic agent of these diseases is not known an attempt was made to determine whether any relationship could be established between them.

Uveitis was observed in 2 of a group of 83 patients with rheumatoid arthritis, and in a group of 63 patients with uveitis, rheumatoid arthritis was observed in 2, an incidence of 2.5 and 3.2 per cent, respectively. Eighty blood cultures were made for 75 patients, 43 of whom had uveitis. In only two cultures were bacteria observed, a hemolytic form of Staphylococcus albus in a case of uveitis and a nonhemolytic form in a case of chorioretinitis.

Thirty-five specimens of anterior chamber fluid from 33 patients, 27 with uveitis, were cultured on various mediums under aerobic and under anaerobic conditions. The cultures yielded no growth.

The predominating organisms of the nasopharynx of patients with uveitis were similar to those isolated from patients with other ocular diseases.

No organisms like those causing pleuropneumonia and no other filtrable agents were isolated from the aqueous or from filtered nasopharyngeal washing of 16 patients with inflammatory ocular diseases.

Of 58 patients with chronic inflammatory ocular disease studied for evidence of undulant fever, 3 had a positive intracutaneous reaction and 1 an agglutination titer of 1 : 40.

No microbial agent was consistently isolated, nor was any filtrable virus recovered from these patients.

DISCUSSION

DR. W. L. BENEDICT, Rochester, Minn.: The results of bacteriologic investigations on patients with rheumatoid arthritis as reported by Dr. Berens parallel investigations that have been made elsewhere and closely resemble those made on a series of patients at the Mayo Clinic. It is somewhat difficult to show that rheumatoid arthritis is a bacterial disease, and it is still more difficult to isolate an organism and to get consistent bacteriologic growths.

I should like to ask if the cultural studies were made during any particular stage of the arthritis, whether the cultures were repeated at different stages and whether any substance was made from the cultures by which the sensitivity of the patient was tested.

DR. EDWARD JACKSON, Denver: It must be realized that this is an era of bacteriologic study; and in the concentration of thought in the direction of bacteriologic factors other possible avenues of discovery are being neglected. These other avenues of progress must be opened up. Some of them are physiologic.

DR. SIDNEY ROTHBARD, New York (by invitation): There is a general impression among clinical investigators that chronic uveitis and rheumatoid arthritis are closely allied diseases. This impression, unfortunately, is not based on satisfactory statistical evidence. However, these conditions do occur together in about 4 per cent of instances. Clinically, rheumatoid arthritis and uveitis are chronic recurring diseases which frequently occur in the same age groups. The etiologic agent is unknown, and a form of therapy specific for both ailments is lacking.

During our laboratory studies, experiments were performed which gave a clearer insight into the pathogenesis of infectious arthritis and iritis. They explained why both conditions may occur in association with certain infectious diseases. Although the infectious nature of chronic uveitis and of rheumatoid arthritis is open to question, as Dr. Jackson has pointed out, the experimental observations may be applicable to the diseases under consideration. Histologic examination of sections of the eyes and the joints of large numbers of rabbits given injections of hemolytic streptococci demonstrated that when cyclitis or arthritis occurs the synovial villi and the ciliary processes are the most frequent and usually the primary sites of inflammation. Bacteria were found in the capillaries of the ciliary processes or in the synovial villi when either the eye or the joint was involved. A localized synovitis or iridocyclitis is brought about by the localization of bacteria in the finger-like synovial villi and ciliary processes. Laboratory observations of this nature suggest a close relationship of uveitis and infectious arthritis.

In answer to Dr. Benedict: Multiple cultures of the blood were made for many of the patients with uveitis or arthritis, but no consistent etiologic agent was found. The patients were for the most part in the active stages of their diseases. The sedimentation rates were elevated, and the joints or the eyes were acutely or subacutely inflamed. Cutaneous tests for hypersensitivity were made with hemolytic streptococcus filtrates or vaccines. Agglutinin tests against the hemolytic streptococcus were also performed on patients' serum. The results of these procedures in patients with uveitis were essentially negative.

In reply to Dr. Jackson I would say that he implied that because this is an age of bacteriology etiologic factors other than bacteriologic ones may be overlooked. This may be true, but deficiency states, climatic conditions and trauma as possible etiologic factors have been studied by numerous investigators. In our work only cultural and immunologic studies were made. However, vitamin deficiency states, adverse climatic conditions and the effect of roentgen rays have all been studied experimentally in an effort to gain an insight into the possible mechanism of arthritis and of uveitis in man.

Gonococcic Conjunctivitis: A Comparison of Sulfanilamide, Sulfapyridine and Sulfathiazole in the Treatment of One Hundred and Twenty Patients. Dr. Philip Meriwether Lewis, Memphis, Tenn.

A review was given of the literature concerning the treatment of gonococcic conjunctivitis with sulfanilamide and its related compounds. The 120 patients on whom the paper was based were treated in the past four years in the isolation department of the John Gaston Hospital, in Memphis, Tenn. The results in 50 patients treated by the usual methods before the sulfanilamide era were compared with those in 90 patients treated with sulfanilamide, 22 treated with sulfapyridine (2-[paraaminobenesulfonamido]-pyridine) and 8 treated with sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole).

The initial dose given was usually about ⅓ grain (0.2 Gm.) per pound of body weight. This was followed every four hours by an amount sufficient to give a total per twenty-four hours of from ½ to 1⅕ grains (0.3 to 0.7 Gm.) per pound. Local treatment consisted of the application of ice compresses until the edema was reduced. Irrigations of cool boric acid solution were administered and were followed by instillation of a 25 per cent solution of mild silver protein or (a more recent and beneficial drug) sodium sulfathiazole in a 5 per cent solution. This treatment was administered every two hours in cases of severe involvement and at four hour intervals in cases of milder involvement.

The most rapid cures were obtained with sulfapyridine, but this drug is not as well tolerated as sulfathiazole. The latter was definitely superior to sulfanilamide. The average number of days for cure was: (*a*) without sulfonamide therapy (50 cases) seventeen and three-tenths days, (*b*) with sulfanilamide (90 cases) five and four-tenths days, (*c*) with sulfapyridine (22 cases) two and fifty-seven one hundredth days and (*d*) with sulfathiazole (8 cases) four days. A severe toxic reaction occurred in only 1 case, in which too large a dose was given.

The author feels that in every case of gonococcic conjunctivitis adequate systemic treatment with sulfapyridine or sulfathiazole should be administered immediately.

DISCUSSION

Dr. Paul A. Chandler, Boston: It is well known that there are various strains of the gonococcus, and the physicians who treat urethritis due to this organism report varying results with sulfanilamide and its derivatives Some patients are cured quickly, whereas others do not

respond so well. It is possible that different strains of the organism are being dealt with.

DR. H. M. LANGDON, Philadelphia: I had an experience with 3 patients treated with sulfathiazole which conforms to the observation Dr. Lewis made in 1 case, that is that sodium sulfathiazole when used locally as an adjuvant is of great help. Of these patients 2 had a negative culture after two days and 1 a negative culture three days after admission. Sodium sulfathiazole in a 5 per cent solution was administered locally every two hours as an adjuvant to the internal medication and was found of great assistance. I believe that used in this way sulfathiazole is equal or possibly superior to sulfapyridine.

DR. CONRAD BERENS, New York: I should like to ask Dr. Lewis whether in his cases of recurrent infection—I believe there were 8 in the sulfanilamide group—he tried immunotherapy. I ask this because of Fleming's work. It is known that sulfanilamide and its derivatives are not bactericidal but bacteriostatic drugs, and Fleming has shown that when the patient's immunity is raised to the highest point—when the drug reaches its greatest concentration—the best results are obtained. Did Dr. Lewis use the same drug when the condition relapsed, and did he find that in some cases the action of the same drug was resisted? This question is asked because it is now believed that some organisms become resistant to the bacteriostatic agent.

DR. PHILIP MERIWETHER LEWIS, Memphis, Tenn.: In answer to Dr. Chandler: I doubt that at the John Gaston Hospital there has ever been administered an amount sufficiently large to give a concentration in the blood as high as 20 mg. per hundred cubic centimeters except in 1 case occurring early in the series. In this case an overenthusiastic intern administered 120 grains (7.7 Gm.) as the initial dose and 20 grains (1.3 Gm.) every four hours thereafter. I believe that when a patient is not progressing well under treatment with one of the sulfanilamide compounds it is advisable to use another. Among urologists it is well known that if a patient does not improve with one of the drugs a change to another is often helpful. For example—a number of patients who are resistant to sulfanilamide show rapid improvement with sulfapyridine.

I thoroughly agree with Dr. Langdon as to the value of sodium sulfathiazole used locally as an adjunct. I am now using routinely a 5 per cent solution locally every two hours along with the internal medication.

In reply to Dr. Berens, there were only 2 patients in the sulfanilamide series who had relapses. They were readmitted to the hospital and eventually were cured by means of more intensive medication. There were no relapses with either sulfapyridine or sulfathiazole. Several patients treated with sulfanilamide recovered very slowly. In treating some of these patients foreign protein therapy was used.

New Aspects of Ocular Micro-Organisms Revealed by the Electron Microscope. DR. PERCE DE LONG and DR. ALVIN W. HOWLAND (by invitation), Philadelphia.

A number of organisms commonly occurring in association with infections of the eye have been studied with the electron microscope.

Classification will not be possible until new standards have been established.

DISCUSSION

Dr. Perce De Long, Philadelphia: The electron microscope has opened a field in science hitherto unexplored. Unfortunately, the demands on this instrument have been so great that we were thwarted in our attempts to present something more of an ophthalmologic nature. We had planned to exhibit a study of the vitreous, but the element of time and the inability to prepare material that would withstand the bombardment of the electronic cell, as well as the inability to provide material that would withstand a complete vacuum, defeated us in this project.

However, we did study the vitreous in about 20 animals, including cats, dogs, rabbits and turtles. All presented a similar picture, that is crystallizations but crystallizations of different types. At the present time we are having the crystals studied. We attempted to include areas of the vitreous that would probably embody the hyaloid membrane, but in no case were we able to observe the membrane. We plan to continue our studies and perhaps reach some definite conclusion. We are not able to carry out studies of cellular tissue, for we cannot prepare material thin enough for the electron ray; we are, however, planning to study the cell by dividing it. When it is realized that the ordinary erythrocyte measures 7 microns and that it must be divided into one-seventh parts for the transmission of the electron ray, the difficulty we encountered can be seen.

Dr. Alvin W. Howland, Philadelphia (by invitation): The direct magnification is between 5,000 and 30,000 diameters in the pictures shown. It is not limited to that, however, but may go on up to 500,000 diameters. The only limitation is the practicability of building an instrument that will produce such magnification. It would be unwieldy and would require a very large photographic plate. The instrument presented, therefore, has been selected as the most suitable type.

CANADIAN OPHTHALMOLOGICAL SOCIETY

J. U. Vaillancourt, M.D., *President*

Alexander E. MacDonald, M.D., *Secretary*

Fourth Annual Meeting, Quebec, Sept. 20, 1941

Symposium on Preoperative and Postoperative Cataract

Technical Arrangements of the Operating Room. Dr. A. L. Morgan, Toronto.

The north side of a building is the most desirable location, because it is cooler and light is more diffuse there. Arrangements can easily be made for darkening the room.

The walls should be a pastel shade of green. General illumination should be 20 foot candles or daylight. The area of operation should be illuminated by a spotlight giving 500 candles. The Ophthalmic Institute

at the Presbyterian Hospital in New York city has sixteen ceiling lights in a circle focused at the head of the table. These are supplemented by a Bausch and Lomb operating lamp.

The operating table should be one that can be easily adjusted according to the height of the surgeon.

The instruments should be checked before the operation to make sure that all are on the tray. The order of instruments should be photographed so that the nurse can pick them out from a list. Fixation forceps with a catch gives easier control. The cataract blade should be thin. Suture in the superior rectus muscle is mechanically unsound One should always have an assistant. Care should be taken concerning sterile technic. A mask should cover the nose. If glasses are worn, adhesive tape or a metal band should be used around the upper edge of the mask.

DISCUSSION

Dr. C. A. Campbell, Toronto: I recommend the Sinclair self-retaining speculum as a great help during the operation. I think that canthotomy is a most desirable procedure to provide exposure. It should be more generally employed.

Preoperative Use of Drugs. Dr. F. T. Tooke, Montreal.

Sedatives comprise analgesics, some somnifacients, soporifics and narcotics. Hypnotics as a class represent some somnifacients and soporifics. Many drugs, such as the opium series, have a combined analgesic and hypnotic action, while the bromides and the barbital group are sedatives in the sense that the question of pain is not one to be taken into consideration.

Sedatives are classified as follows:

1. The bromides.
2. The chloral group: chloral hydrate or paraldehyde.
3. The urethane group; the barbital series.
4. The sulfonmethanes: Sulfonmethane-N. F. (sulfonal) and sulfonethylmethane-U. S. P. (trional).
5. The opium series: morphine, codeine, diacetylmorphine (heroin), a preparation containing the hydrochlorides of the alkaloids, principally morphine (pantopan) and dilaudid hydrochloride.

The advantages and more particularly the disadvantages of the drugs, especially those of the barbital group and the opium series, were emphasized. The author stressed the fact that no one drug should be administered for an extended period and also the fact that in order to avoid idiosyncrasies and unfortunate complications a trial dose should be prescribed one or possibly two days before an operation is contemplated. Frequently a little time taken to establish a sense of confidence and cooperation renders sedatives unnecessary.

DISCUSSION

Dr. J. U. Vaillancourt, Quebec: What should the routine practice be with regard to the use of sedatives?

Dr. F. T. Tooke, Montreal: I recommend bridging the psychologic attitude of the patient in order to cultivate confidence. The value of

the administration of any drug depends on the confidence and the cooperation of the patient at the time of the operation. The barbiturates are most valuable, and so in recent years the use of the opium series has been largely discontinued.

Dr. W. G. Fraser, Ottawa: What is the incidence of "barbiturate jag"? I like to have my patients get a good rest, and on several occasions I have deferred the operation until such a rest has been obtained. I believe that complete cooperation is necessary, and it is my practice to rehearse the patient in looking down and so forth. After soluble pentobarbital U. S. P. (pentobarbital sodium) is administered, it should not be necessary to shout. The patient should have a cup of tea three quarters of an hour before the operation.

Dr. R. J. P. McCulloch, Toronto: I deliberately instruct my patients not to cooperate, and I tell them that they have no part to play. I use sedatives extensively and on occasion have had to postpone an operation on account of a "barbiturate jag." I like my patients to be in an untroubled state of mind.

Dr. J. L. Coupal, Ottawa, Ontario: What about the use of alcohol for habitual imbibers of this stimulant?

Dr. A. E. MacDonald, Toronto: I have allowed the use of alcohol preoperatively since an experience some years ago with a frail, neurotic woman. I visited her before she left her room for the operation and found her behind a screen drinking whisky from a bottle. She did remarkably well, was a good patient and made an uneventful recovery.

Dr. W. W. Wright, Toronto: I have found that some patients require sedation, while others do better without it. As a rule I administer the drug the night before and also before the operation so that the patient may have a good sleep on returning to his room.

Sterilization of the Conjunctival Sac Preparatory to Cataract Extraction. Dr. J. A. MacMillan, Montreal.

An operation for cataract is performed only when cultures show the conjunctival sac to be free from pathogenic organisms. A 1 per cent solution of dextrose–beef infusion broth is dropped into the conjunctival sac. Withdrawn fluid is transferred to dextrose broth and blood plate. The results are reported in two days. If pathogens are found, applications of a 1 per cent solution of silver nitrate are given daily, and drops of zinc sulfate or metaphen solution are used. About 30 per cent of the cultures show pathogens. Often negative cultures are not obtained for long periods, the delay necessitating postponement of the operation. Recently, sulfanilamide powder has been used in dusting the conjunctival sac, or a 5 per cent solution of sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) instilled three times a day when the cultures are positive. Negative cultures are reported two days after the procedure. If these drugs have been used, bacteriologists neutralize the effect on cultures with paraaminobenzoic acid. Sulfanilamide has a solvency in saline solution at 37 C. of 1.5 per cent. Sodium sulfathiazole has a solvency of about 30 per cent, but the solution has a p_H of about 10; hence the 5 per cent solution. By this method delay in operation in cases

in which there are pathogenic organisms in the conjunctiva is lessened. although the number of cases is too small and the time too short for dogmatism.

DISCUSSION

Dr. J. U. Vaillancourt, Quebec: I urge that great care be taken in the methods of culture and wish to refer to an early experience in which panophthalmitis resulted two days after extraction and it took a year of steady treatment to clear the conjunctiva of infection before the other eye could be operated on. In the light of modern experience, I remember with amazement the good results achieved in Paris in 1906, when the surgeon used no culture, wore no gown, washed his hands a little, put on his eyeglasses, took a knife out of his pocket and went to work.

Dr. R. E. Mathers, Halifax, Nova Scotia: During a recent visit to one of the New York hospitals, I noted that the surgeon used only a 25 per cent solution of mild protein silver and no culture.

Dr. J. V. V. Nicholls, Montreal: I wish to call attention to the danger of trauma in cultural methods, as the infective microbe may die before transfer from the swab to the medium. The medium should be warmed before it is inoculated. Careful attention to such details gives a higher percentage of positive findings, especially for a microbe as delicate as the pneumococcus.

Dr. W. G. Fraser, Ottawa, Ontario: What about the cauterization of the puncta? At times I have found it necessary to dissect the complete canaliculus. Can satisfactory results be obtained by tying the puncta with a suture?

Dr. W. G. M. Byers, Montreal: I believe that Dr. Buller was the first to tie off the canaliculus. He personally recommended cultures in order to arrive at some remedy to make more certain the sterilization of the conjunctiva, and if it should be proved that such a remedy cannot be achieved, at least one will be aware of the need for caution as far as contacts with the surface and the instruments are concerned. Syringing of the lacrimal sac with saline solution is important when there is irritation of the anterior part of the inferior turbinate.

Dr. S. G. Elliott, Toronto: At the Presbyterian Hospital, in New York, immediate incubation is considered essential. Marmital will show the toxic strains in a few hours. At the New York Eye and Ear Hospital only smears are made. These institutions show results that are apparently equal.

Dr. J. A. MacMillan, Montreal: Cultures are desirable even if they only point out an occasional danger. A warm medium is important and may be achieved by flushing the lower fornix with medium from a fine pipet. I believe it is advisable to remove a soiled canaliculus and in case of doubt to use a large flap as well as to paint the area with a 2 per cent solution of silver nitrate before operation.

Cholesterol and Cataract. Dr. Henri Pichette, Quebec.

It is generally believed that cholesterol and lipids are increased in cataractous lenses. In 32 patients with cataract the medium value

averaged 0.32 per cent. The chief animal sterol was cholesterol, a constituent of all animal cells.

In Herbivora, by the feedings of cholesterol toxic effects are produced from which a condition known as atherosis results; this condition is similar to arteriosclerosis in the human being.

Cholesterol is found in the human body in greater or lesser quantity depending on the age, the sex, the alimentary regimen and the senescent state of the tissues and organs, and the concentration in the blood can be modified by a hyperfatty or hypofatty diet. My co-workers and I verified and controlled these facts by more than 4,000 cholesterol titrations. Our researches on animals, such as rabbits, dogs, lambs and pigs, were corroborative.

The cholesterol is seen in the blood and in the tissues in two forms: free and saponified. Sometimes it is accumulated to form real masses, as in xanthelasma and arcus senilis, but most of the time it remains in a fine suspension, in a real colloidal state, and it is accumulated as such in various organs.

In the lens the cholesterol can be precipitated as crystals or a soap, or it can remain as a colloid which can give rise to a gel or a sol.

If in the blood or in the interstitial liquid the concentration of heterogenic substances, such as sugar, carbohydrates, proteins, minerals, lipids or cholesterol, becomes too high, the normal equilibrium is broken and the supersaturation gives a precipitation, a flocculation or a gel formation. These physicochemical modifications give rise to particular phenomena, which are called pathologic, and these are frequently found at the lens as variations in refraction modifications of transparency, opacities and total sclerosis.

The pathogenesis of lesions of the eye should be considered in relation to the general dysfunctions of the metabolism, and if one recalls that the metabolism is a mere expression of the physicochemical variations that the food products undergo in the organism from their ingestion to their final transformation into specific energies, one will more easily understand the role of food absorption in the genesis of the so-called pathologic lesions.

DISCUSSION

DR. J. U. VAILLANCOURT, Quebec: This paper gives in condensed form the results of ten years of investigation. It may throw some light on the problem of congenital cataract, which condition is so frequently accompanied by mental deficiency. With the whole chemical set-up of the body altered, what treatment is advised before operation?

DR. HENRI PICHETTE, Quebec: The close relation between the presence of fats and cholesterol suggests that fats be eliminated before operation. It has been found that this gives surprisingly good and rapid results.

Atoxic Cataract. DR. F. BADEAUX, Montreal.

The patient was a boy 16 years of age showing eczema of the face. He was first seen in 1937, when he came to have his eyes tested. There was no lesion of the lenses and no chronic dermatitis.

In 1940 he came for another test of his eyes. The vision was 20/30 in the right eye and 20/20 in the left eye with correction. The lenses

presented iridescent vacuoles and precipitates at the anterior and the posterior poles. All these changes were immediately beneath the capsule.

There was also striation of the lens fibers.

The blood tests all gave normal results, but still it is believed that there is an allergic basis for the changes described.

The family history disclosed that a brother and a sister have eczema.

Cataract with Parathyroid Insufficiency. Dr. F. Badeaux, Montreal.

A woman 42 years of age was examined in 1938 because of a decrease in vision in both eyes. This trouble began in 1936, three years after an operation for goiter. Besides the ocular lesions, the patient showed the Trousseau sign of the fingers (flexion). She was operated on for cataract. The lenses showed so-called complicated cataract. This was attributed to a badly performed operation for goiter. The parathyroids must have been removed with the thyroid gland. Calcium was prescribed, and all the signs of parathyroidal insufficiency disappeared.

DISCUSSION

Dr. A. L. Morgan, Toronto: What about the condition of the posterior capsule?

Dr. F. Badeaux, Montreal: With regard to the first case, polychrome rays are to be seen anteriorly and posteriorly, and vacuoles are present. I prefer to dislocate only with the Elschnig forceps and then to express the lens in capsule, as the instrument in a full extraction puts too much pressure on the lips of the wound, with danger of loss of vitreous. It is possible that parathyroid deficiency is present in some types of juvenile cataract.

Epithelial Cysts in the Anterior Chamber Following Cataract Extraction. (Lantern Demonstration). Dr. B. K. Johnston, Montreal.

Epithelial cysts occurred in 3 of 30 eyes that had cataract extraction (from the collection of the Royal Victoria Hospital, Montreal):

1. Enucleation two years after extraction: upper half of the cornea opaque; increased tension; lens capsule in the wound; epithelium extending from the surface lining back of the cornea.

2. Enucleation one year after extraction: cornea milky white and streaky; globe shrunken; epithelium penetrating from the surface, forming an epithelial cyst and lining half the anterior chamber.

3. Enucleation two years after cataract extraction: history of unexplained interstitial keratitis, corneal vascularization and hypotony; development finally of endophthalmitis and hypopyon; epithelium in sections lining the anterior chamber and the iris except the pupillary area.

Such cases emphasize the need for: (1) a careful washing out of the wound, (2) corneal sutures and (3) intracapsular extraction.

Epithelial Invasion of the Anterior Chamber. (Lantern Demonstration.) Dr. T. H. Hodgson, Toronto.

Faulty closure of the wound with delayed formation of the anterior chamber provides a favorable state for the spread of epithelium into

the anterior chamber. Serial sections from an eye removed for this condition were shown, and in one of these sections a core of epithelium was seen to extend through the entire thickness of the cornea, linking the epithelium on the surface with that in the anterior chamber and indicating the mode of extension. Glaucoma had not developed in this case. The possibility of epithelization of the anterior chamber developing in certain cases should be kept in mind because if the diagnosis can be made, early radiation therapy can be tried with some hope of success.

DISCUSSION

DR. J. A. MACMILLAN, Montreal: I wish to emphasize the importance of keeping in mind the fact that in some cases there may be hypotony rather than developing glaucoma.

Postoperative Care. DR. H. FOLGER, Kingston, Ontario.

The author pointed out that preoperative and operative procedures are closely related to postoperative care. It was suggested that as much freedom of movement be given to the cataract patient postoperatively as is consistent with safety. The use of sutures and the type of dressing were discussed.

DISCUSSION

DR. C. A. CAMPBELL, Toronto: I wish to call attention to the instructions given regarding postoperative care at the Western Hospital, in Toronto, and I suggest that every nurse have a copy. The patient in a public ward has the benefit of a specialized nurse, while the private patient has a nurse who attends only an occasional patient after operation for cataract.

DR. R. J. P. MCCULLOCH, Toronto: I do not have a copy of the instructions with me, but I advise the avoidance of all possible damage, especially to the endothelium.

DR. W. G. M. BYERS, Montreal: I wish to call attention to the favorable statistics of the Fuchs Clinic when all the difficult cases were in charge of the chief, who permitted the patient to walk back to his ward after an operation for cataract.

DR. A. L. MORGAN, Toronto: I wish to report that in a patient who vomited after operation the upper lid was found in the lips of the wound. Since that time I have used a lid suture which can be inserted painlessly after injection of the lids by the Van Lint method. On the fifth day the lids are slightly separated and atropine ointment is inserted.

DR. W. G. FRASER, Ottawa: I suggest using a drop of a 25 per cent solution of mild silver protein after the cataract operation in order to show up the lips of the conjunctiva, which are pinched together in several places, instead of inserting sutures. A Hess forceps will give good adherence of the edges, and even in a soiled conjunctiva infection is prevented.

DR. J. U. VAILLANCOURT, Quebec: A patient of mine was found out in the street immediately after a cataract operation, and all his dressings had been removed. The surgical result was good, however.

DR. W. W. WRIGHT, Toronto: I know of a patient who sued because of severe damage to her eyes which followed the feeding by a nurse of soup that was too hot. As a result the patient had coughed and lost

the eye because of prolapsed iris. She also lost the sight of the other eye as a result of sympathetic ophthalmia.

Dr. A. G. McAuley, Montreal: I find that most complications following operations for cataract result from squeezing the lids. I prefer to operate with the patient on a Gatch bed, and I elevate him to a half-sitting position after returning him to his room. I permit bathroom privileges to my patients.

Dr. W. G. M. Byers, Montreal: There is little danger of hemorrhage during the first few hours. I wish to report the case of a missionary who disappeared immediately after the operation and returned four years later, at which time his vision was 6/6 with correction.

Dr. A. E. MacDonald, Toronto: These exceptions prove the rule that constant attention should be used to prevent exertion on the part of the patient. There usually is no need for an evacuation for three days when the patient is on a light diet with only water for the first day. Vomiting rarely results if milk, beverages with cream, carbonated drinks and fruit juices are avoided. The nurse should speak immediately to the patient on his awakening from any sleep.

Postoperative Hemorrhage. Dr. R. J. P. McCulloch, Toronto.

Use of the intracapsular operation has increased the frequency of postoperative hemorrhage. It occurs after 20 per cent of operations for cataract. In most cases the amount is slight and absorption is complete. In some cases, however, opacities of the vitreous may result.

Possible sources of bleeding are: (1) the sclerocorneal wound, (2) the conjunctival wound and (3) the wound of the iris, or bleeding may result from some blood dyscrasia.

Actually, the sclerocorneal wound is almost always the source, and the breaking down of this wound by the reforming intraocular pressure is the cause.

A spasm of the orbicularis muscle during a reaction of the patient to light or fear of pain and the downward pull of the inferior rectus muscle help to burst open the wound.

To lessen the frequency of this complication (1) suture the wound adequately, (2) eliminate after-dressings for the first week except for some specific cause and (3) have the patient out of bed the second day to lessen the amount of use of the inferior rectus muscle.

DISCUSSION

Dr. C. A. Campbell, Toronto: What technic is used for suturing?

Dr. A. L. Morgan, Toronto: I use two sutures, one over each pillar into the cornea and the sclera. Some are inserted before and some after section.

Dr. W. G. Fraser, Ottawa: I have not noticed any poor visual results following hyphemia. I use a peripheral iridectomy and instill physostigmine at the time of operation. Should a prolapse occur, the part must be excised early. I have had no prolapse in 70 cases; however, I usually instill atropine on the third day.

Dr. P. B. McFarlane, Hamilton, Ontario: The position of the patient is important, and movement of the eyes to follow sounds results

in a gaping of the lips of the wound. The patient should be raised so that he can look only straight ahead, and a hole in the mask over the eye not operated on helps.

DR. A. J. ELLIOTT, Toronto: At the Presbyterian Hospital, in New York city, a review has shown that 21 per cent of the patients who have undergone operation for cataract have had postoperative hemorrhage. The retrobulbar injection had no effect on this; neither had high blood pressure. Diabetes and a vitamin C deficiency have been found to have no relation to hemorrhage; neither has capillary fragility or the bleeding or the clotting time. The amount of hemorrhage was severe in 12 per cent of the patients, and only half of them suffered pain. New dressings were not applied until the fifth day.

DR. A. E. MACDONALD, Toronto: I recently have seen three postoperative hemorrhages following nightmares, and in 1 instance secondary glaucoma supervened.

DR. R. J. P. MCCULLOCH, Toronto: I have seen a hemorrhage occur at the time of the first dressing. A fine red line appeared at the cut conjunctival edge. I make my section by starting in the usual manner, but I stop at about the 11 to 1 o'clock line and insert two sutures on each side. The section is completed with scissors, and two more sutures are inserted.

Miscellaneous Reports

Ocular Examination for Air Crew in the R. C. A. F. FLIGHT LIEUTENANT J. NICHOLLS, M.D., Montreal.

The author divided the examination into tests of (1) visual acuity, (2) color vision, (3) ocular muscle balance and (4) other factors, such as fields of vision, fundi and extraocular disturbances.

The incidence of unusual visual conditions causing rejection was discussed in a paper that cannot well be abstracted.

Ophthalmology in the Navy. SURGEON LIEUTENANT COMMANDER E. A. AMOS, M.D., Montreal.

A short review was presented of the most frequently encountered ocular conditions seen in the Canadian naval service, with their relative incidence, as compared with those encountered in civilian life.

The ocular findings in cases of ariboflavinosis, especially those observed with the slit lamp, were presented for three groups of men living on different diets: "sea going," "barracks" and a miscellaneous group. The decidedly higher percentage of findings observed with the slit lamp in the "sea-going" group was noted, and the therapeutic results of the oral administration of pure riboflavin, 4 mg. daily over a period of eight to ten days, were reported. The clinical appearance was described, and the case histories were quoted.

DISCUSSION

DR. W. G. M. BYERS, Montreal: Was a Y-shaped arrangement of the capillaries found in the cornea, and was it possible to demonstrate loops in the cornea in cases of ariboflavinosis? The presence of other

symptoms, such as scales at the corner of the mouth, is important in the diagnosis of this condition. Were the ocular findings due to a deficiency in riboflavin alone, and what results were found with treatment consisting of the administration of riboflavin?

DR. J. NICHOLLS, Montreal: Was riboflavin in 15 mg. doses tried? By the Krause classification, group 1 was found to be of interest in air force work. The influence of gastric acidity is important.

DR. A. E. MACDONALD, Toronto: Among 134 patients examined at Halifax, Nova Scotia, there were several cases of severe ariboflavinosis according to the present diagnostic technic with the slit lamp; a greater incidence was found in men of the Royal Navy who had been at sea for longer periods. Among 100 men who had been subsisting on a carefully checked diet, there were a few cases of mild corneal vascularization. Chemosis, glossitis and gastric symptoms were looked for.

DR. A. L. MORGAN, Toronto: Are the older officers examined regularly? Are glasses a handicap in the navy and why? In my lake-racing crew there are several men who have visual defects, but in spite of this the crew won the group contest.

Traumatic and Sympathetic Glaucoma. DR. JULES BRAULT, Montreal.

From the study of the clinical cases presented, it was possible to draw the following conclusions:

1. The trauma to the eyeball is apt to produce a disequilibrium of the regulator nervous system of the ophthalmotonus, which manifests itself by hypotonia or hypertonia of the wounded eye.

2. In contusions of the eyeball one should always fear the rise of tension and the appearance of secondary glaucoma. For this reason one should use mydriatic agents with great care. In the first case reported the use of atropine might have been an adjuvant cause of glaucoma.

3. Finally, another clinical fact, and the most striking of all, is the very sympathetic hypertonia which was observed in the 4 cases. In the first 3 the hypertonia complicated traumatic secondary glaucoma. In the fourth it seemed sustained by a nervous irritation from a neoplasm of the choroid of the fellow eye. Another outstanding feature to notice is that reflex hypertonia diminishes with the treatment of the exciting eye.

It is clear from the study of these 4 cases that one must admit the existence of sympathetic glaucoma or of reflex hypertonia.

I have since observed more closely our clinical cases of post-traumatic secondary glaucoma, especially those cases in which the condition developed after the appearance of an intraocular foreign body associated with a severe injury of the anterior segment. In nearly all cases of traumatic glaucoma I have noticed a rise of tension in the fellow eye but never a rise as high as in the cases reported.

It seems that in cases of contusions of the eye there is transmission of irritation from one eye to the other, followed by a bilateral ophthalmotonic disequilibrium, with maximum tensity in the wounded eye. This

change in tension would show itself either by hypotonia or by hypertonia. It is not uncommon that hypertension succeeds hypotension or vice versa.

The Vesicant Gases and Ocular Lesions. Dr. H. M. Macrae, Toronto.

The action of a 10 per cent solution of mustard gas as a droplet contaminator in the eyes of rabbits has been studied. The sequelae are similar to those from a drop of full strength solution in the human eye. Congestion, edema, exfoliation of the epithelium of the cornea and interstitial keratitis are the constant changes noted. Some corneal opacification remains permanently. It is now known that in cases of apparently healed mustard gas contamination a type of neuropathic keratitis which is not seen as a result of any other chemical burn often develops in from fifteen to twenty years.

Retrobulbar Injection of Procaine Hydrochloride and Alcohol in the Practice of Ophthalmology. Dr. L. A. Carte, Quebec.

Alcohol and procaine hydrochloride injected into the retrobulbar area could play a greater part in ocular therapeutics than they do. The technic is as follows: First inject 2 cc. of a 2 per cent solution of procaine hydrochloride, and one minute later inject 1 cc. of a 30 per cent to 20 per cent solution of ethyl alcohol. The injection is not painful, and the sedative effects are immediate. The injections are used for ocular pain as well as to reduce the tension in acute and subacute glaucoma. In painful conditions of the anterior segment, the injections are particularly indicated.

Optical Correction of Aphakia. Dr. Emile Blain, Montreal.

Aphakia results in loss of accommodation, a surgical astigmatism of about + 2.00 D. and anisometropia. The field of vision is limited by the strong lens. Glasses should be ordered after the sixtieth day only if the vision with correction is better than that in the other eye. Bifocals should be well centered; the glasses should be at the same distance from the eye as in the trial frame.

Book Reviews

Cuestiones oftalmologicas. By Manuel Marquez, Professor of Ophthalmology, Faculty of Medicine, University of Mexico. Pp. 368, with numerous illustrations. Mexico City: Fondo de Cultura Economica, 1942.

This book is the outcome of a series of lectures given in the Faculty of Medicine of the University of Mexico during the summer of 1939 by Professor Marquez, who became established in Mexico after the end of the Civil War in Spain. The twenty lectures included are recapitulations of subject matter which has already been published and in which Professor Marquez has a claim for originality. The volume is well printed and illustrated and shows the same editorial care as the same author's textbook of ophthalmology.

The twenty-two lectures cover a great field, from geometric optics to neurology of the eye and from the anatomy and physiology of the ocular movements and of the pupil to Cajal's work and operations on the iris and lids. Each chapter has a brief summary in English which makes the book accessible to American readers.

Lesson 3 deals with dioptric measurements in optics. The author states that it is often convenient to replace ordinary measurements in optics by their reciprocals, just as the curvature of the surface is best expressed by the reciprocal of its radius. The subject is exhaustively described. Lesson 4 deals with the well known facts on Purkinje-Sanson images, especially the second and third. This subject would seem to have lost much of its importance since the advent of slit lamp microscopy, which permits direct observation of the optical section of the cornea and the lens. In the fifth lesson the author develops his idea of the correction of myopia by a system of convex glasses. With this it is possible in some cases to obtain better vision, because the images which this system forms always appear in the plane of the punctum remotum of the patient and increase the size of the images produced. It may be of practical value in cases of high myopia with fundus lesions.

The sixth lesson concerns the theory and practice of skiascopy. The author advocates use of a concave mirror of 1 meter focus instead of the plane mirror used in America. He describes two neutral points instead of one. The first is placed at the level of the patient's pupil and does not move. The observer should disregard it and use the second neutral point, which is produced by the intersection of the rays of light at the level of his own pupil as reflected from the patient's retina. Professor Marquez does not mention the theory of skiascopy of Parent and Troncoso, which so practically explains the movement of the shadow by the displacement of the field of illumination over the field of observation in the retina, as seen by the observer in direct and inverted images.

Lecture 7 deals with the question of biastigmatism and its correction by cylindric combinations. This subject has been extensively treated by Marquez in many other papers, but not all authors agree with his conclusions. Lessons 8 and 9 describe the chiasmatic decussation in

the animal series. Starting from the work of Cajal, Marquez discusses what would happen in a cyclopic eye, in which there would be no chiasm.

Three lessons deal extensively with the dynamics of ocular movements, normal and pathologic, and their nervous control and with the changes undergone by the peripheral, cortical and mesocephalic neurons. These subjects are well treated and illustrated, and the material will be read with profit by students of ocular neurology.

There are two historical chapters in the book. One refers to the work of Cajal in neuro-ophthalmology and the second to the painter El Greco, whose elongated figures were supposedly due to his astigmatism, an opinion the author does not share.

This book is interesting and will be of service to those students who want to delve into the subjects of neuro-ophthalmology and geometric optics.

M. U. TRONCOSO.

Allergy in Clinical Practice. By staff members of the Cleveland Clinic under the direction of Russell L. Haden, M.D.; edited by J. Warrick Thomas, M.D. Price, $5. Pp. 354, with 92 illustrations, 14 in color. Philadelphia: J. B. Lippincott Company, 1941.

After an introduction by Dr. Russell L. Haden on allergy as a factor in general medicine, the book begins with a general chapter by Dr. J. Warrick Thomas on the examination of the patient, comprising the history, physical examination, investigation, sensitization studies and a summary of the therapeutic program.

Then follows consideration of bronchial asthma, hay fever, perennial nasal allergy, allergic bronchitis, bronchiectasis, contact dermatitis, atropic dermatitis, drug eruptions, allergic manifestations of superficial fungous infections, urticaria and angioneurotic edema, gastrointestinal allergy, ocular manifestations of allergy, migraine and other allergic headaches, endocrine considerations in the allergic patient, uncommon manifestations of allergy and allergy in clinical practice.

The chapter on ocular manifestations, which is of special interest to readers of these ARCHIVES, was written by Dr. A. D. Ruedemann and treats of contact dermatitis, blepharitis, styes, conjunctivitis, iritis, cataracts, opacities of the vitreous, retinal changes, retrobulbar neuritis and myopia. The author emphasizes that every case of progressive myopia and keratoconus should be carefully investigated for allergic factors in the causation. A number of illustrated case histories are added. In the summary Dr. Ruedemann says that the most common ocular symptoms in allergic conditions are photophobia and lacrimation, with a less frequent occurrence of blepharospasm; the most common sign is edema, with swelling of the lower lid and congestion of the affected part, and every case of ocular allergy is associated with an allergic condition elsewhere in the body.

Hypersensitivity, from its frequent occurrence in every physician's practice, is now being recognized as of great importance in the causation of disease. The reader will appreciate the clear and lucid manner in which the subject is presented. The aid of specialists in each branch of medicine is enlisted to solve the frequent difficulties in the diagnosis of allergic conditions. The book can be unreservedly commended.

ARNOLD KNAPP.

A Handbook of Ocular Therapeutics. By Sanford R. Gifford, M.D. Third edition. Price, $4. Pp. 410, with 69 engravings. Philadelphia: Lea & Febiger, 1942.

Dr. Gifford's excellent handbook has undergone a thorough revision in this new edition. With painstaking thoroughness it has been brought up to date, and the reader may be sure to obtain reliable information on new remedies and new methods of treatment. The new chapter on the pharmacology of drugs affecting the intraocular muscles will be found most instructive and useful. This gives an explanation of the action of the newer drugs which through the parasympathetic and the sympathetic nerves affect the pupil and the ocular pressure. The advantages of vitamin therapy in the treatment of certain ocular conditions are described with a full realization that this subject is far from understood at the present day. Another new remedy which seems most promising is sulfanilamide and its derivatives, and the author contributes an excellent chapter on the various drugs of this group.

In the chapter on physical therapy, contact irradiation for retinocytoma and the use of beta emanations in the treatment of tuberculosis of the anterior segment of the eyeball constitute the advances which are fully described.

Many other changes that make for improvement can be noted, and the new illustrations are helpful. The book cannot be too warmly recommended; it is an essential to every practicing ophthalmologist.

ARNOLD KNAPP.

The March of Medicine. New York Academy of Medicine Lectures to the Laity, no. VI. Price, $2. Pp. 154. New York: Columbia University Press, 1941.

The lectures have a foreword by Dr. Malcolm Goodridge, president of the New York Academy of Medicine, and an introduction by Dr. Haven Emerson. The subjects of the six lectures are as follows:

I. Humanism and Science, the Linsly R. Williams Memorial Lecture, Alan Gregg, M.D. II. Paracelsus in the Light of Four Hundred Years, Henry E. Sigerist, M.D. III. Psychiatry and the Normal Life, William Healy, M.D. IV. Philosophy as Therapy, Irwin Edman, Ph.D. V. The Promise of Endocrinology, Oscar Riddle, Ph. D. VI. What We Do Know About Cancer, Francis Carter Wood, M.D.

The subjects of these lectures are matters of great interest to the layman and to the physician. Both are indebted to the academy for issuing the lectures in a permanent form, by which the circle of readers will be greatly enlarged. The book making is excellent, and an unusually complete index concludes the little volume.

ARNOLD KNAPP.

Directory of Ophthalmologic Societies *

INTERNATIONAL

International Association for Prevention of Blindness

President: Dr. P. Bailliart, 66 Boulevard Saint-Michel, Paris, 6e, France.
Secretary-General: Prof. M. Van Duyse, Université de Gand, Gand, Prov. Ostflandern, Belgium.
All correspondence should be addressed to the Secretariat, 66 Boulevard Saint-Michel, Paris, 6e, France.

International Ophthalmologic Congress

President: Prof. Nordenson, Serafimerlasarettet, Stockholm, Sweden.
Secretary: Dr. Ehlers, Jerbanenegade 41, Copenhagen, Denmark.

International Organization Against Trachoma

President: Dr. A. F. MacCallan, 17 Horseferry Rd., London, England.

Pan-American Congress of Ophthalmology

President: Dr. Harry S. Gradle, 58 E. Washington St., Chicago.
Executive Secretaries: Dr. Conrad Berens, 35 E. 70th St., New York. Dr. M. E. Alvaro, 1511 Consolacao, São Paulo, Brazil.

FOREIGN

All-India Ophthalmological Society

President: Dr. B. K. Narayan Rao, Minto Ophthalmic Hospital, Bangalore.
Secretary: Dr. G. Zachariah, Flitcham, Marshall's Rd., Madras.

British Medical Association, Section on Ophthalmology

President: Dr. W. Clark Souter, 9 Albyn Pl., Aberdeen, Scotland.
Secretary: Dr. Frederick Ridley, 12 Wimpole St., London, W. 1.

Chinese Ophthalmology Society

President: Dr. C. H. Chou, 363 Avenue Haig, Shanghai.
Secretary: Dr. F. S. Tsang, 221 Foochow Rd., Shanghai.

Chinese Ophthalmological Society of Peiping

President: Dr. H. T. Pi, Peiping Union Medical College, Peiping.
Secretary: Dr. C. K. Lin, 180 Hsi-Lo-yen, Chienmeng, Peiping.
Place: Peiping Union Medical College, Peiping. Time: Last Friday of each month.

German Ophthalmological Society

President: Prof. W. Lohlein, Berlin.
Secretary: Prof. E. Engelking, Heidelberg.

Hungarian Ophthalmological Society

President: Prof. I. Iwre, Budapest.
Assistant Secretary: Dr. Stephen de Grósz, University Eye Hospital, Mária-utca 39, Budapest.
All correspondence should be addressed to the Assistant Secretary.

Midland Ophthalmological Society

President: Dr. W. Niccol, 4 College Green, Gloucester, England.
Secretary: Mr. T. Harrison Butler, 61 Newhall St., Birmingham 3, England.
Place: Birmingham and Midland Eye Hospital.

* Secretaries of societies are requested to furnish the information necessary to make this list complete and keep it up to date.

NORTH OF ENGLAND OPHTHALMOLOGICAL SOCIETY

President: Dr. A. MacRae, 6 Jesmond Rd., Newcastle-upon-Tyne, England.
Secretary: Dr. Percival J. Hay, 350 Glossop Rd., Sheffield 10, England.
Place: Manchester, Bradford, Leeds, Newcastle-upon-Tyne, Liverpool and Sheffield, in rotation. Time: October to April.

OPHTHALMOLOGICAL SOCIETY OF AUSTRALIA

President: Dr. A. James Flynn, 135 Macquarie St., Sydney.
Secretary: Dr. D. Williams, 193 Macquarie St., Sydney.

OPHTHALMOLOGICAL SOCIETY OF EGYPT

President: Prof. Dr. Mohammed Mahfouz Bey, Government Hospital, Alexandria.
Secretary: Dr. Mohammed Khalil, 4 Baehler St., Cairo.
All correspondence should be addressed to the secretary, Dr. Mohammed Khalil.

OPHTHALMOLOGICAL SOCIETY OF THE UNITED KINGDOM

President: Mr. T. Harrison Butler, 61 Newhall St., Birmingham 3, England.
Secretary: Mr. L. H. Savin, 7 Queen St., London, W. 1, England.

OPHTHALMOLOGY SOCIETY OF BOMBAY

President: Dr. D. D. Sathaye, 127 Girgaum Rd., Bombay 4, India.
Secretary: Dr. H. D. Dastur, Dadar, Bombay 14, India.
Place: H. B. A. Free Ophthalmic Hospital, Parel, Bombay 12. Time: First Friday of every month.

OXFORD OPHTHALMOLOGICAL CONGRESS

Master: Dr. Percival J. Hay, 350 Glossop Rd., Sheffield 10, England.
Secretary-Treasurer: Dr. F. A. Anderson, 12 St. John's Hill, Shrewsbury, England.

PALESTINE OPHTHALMOLOGICAL SOCIETY

President: Dr. Arieh Feigenbaum, Abyssinian St. 15, Jerusalem.
Secretary: Dr. E. Sinai, Tel Aviv.

POLISH OPHTHALMOLOGICAL SOCIETY

President: Dr. W. Kapuściński, 2 Waly Batorego, Poznań.
Secretary: Dr. J. Sobański, Lindley'a 4, Warsaw.
Place: Lindley'a 4, Warsaw.

ROYAL SOCIETY OF MEDICINE, SECTION OF OPHTHALMOLOGY

President: Dr. A. J. Ballantyne, 11 Sandyford Pl., Glasgow, C. 3, Scotland.
Secretary: Dr. C. Dee Shapland, 15 Devonshire Pl., London, W. 1, England.

SÃO PAULO SOCIETY OF OPHTHALMOLOGY

President: Dr. Jacques Tupinambo, 258 Inglezes, São Paulo, Brazil.
Secretary: Dr. Silvio de Almeida Toledo, Enfermaria Santa Luzia, Santa Casa de Misericordia, Cezario Motta St.—112, São Paulo, Brazil.

SOCIEDAD OFTALMOLOGIA DEL LITORAL, ROSARIO (ARGENTINA)

President: Prof. Dr. Carlos Weskamp, Laprida 1159, Rosario.
Secretary: Dr. Juan M. Vila Ortiz, Córdoba 1433, Rosario.
Place: Rosario. Time: Last Saturday of every month, April to November, inclusive.
All correspondence should be addressed to the President.

SOCIEDADE DE OPHTHALMOLOGIA E OTO RHINO-LARYNGOLOGIA DA BAHIA

President: Dr. Theonilo Amorim, Barra Avenida, Bahia, Brazil.
Secretary: Dr. Adroaldo de Alencar, Brazil.
All correspondence should be addressed to the President.

SOCIETÀ OFTALMOLOGICA ITALIANA

President: Prof. Dott. Giuseppe Ovio, Ophthalmological Clinic, University of Rome, Rome.
Secretary: Prof. Dott. Epimaco Leonardi, Via del Gianicolo, 1, Rome.

Société Française d'Ophtalmologie

Secretary: Dr. René Onfray, 6 Avenue de la Motte Picquet, Paris, 7e.

Society of Swedish Ophthalmologists

President: Prof. K. G. Ploman, Stockholm.
Secretary: Dr. K. O. Granström, Södermalmstorg 4 Ill tr., Stockholm, Sö.

Tel Aviv Ophthalmological Society

President: Dr. D. Arieh-Friedman, 96 Allenby St., Tel Aviv, Palestine.
Secretary: Dr. Sadger Max, 9 Bialik St., Tel Aviv, Palestine.

NATIONAL

American Medical Association, Scientific Assembly, Section on Ophthalmology

Chairman: Dr. Lawrence T. Post, 508 N. Grand Blvd., St. Louis, Mo.
Secretary: Dr. Derrick Vail, 441 Vine St., Cincinnati.
Place: Atlantic City. Time: June 8-12, 1942.

American Academy of Ophthalmology and Otolaryngology, Section on Ophthalmology

President: Dr. Ralph I. Lloyd, 14–8th Ave., Brooklyn.
President-Elect: Dr. James A. Babbitt, 1912 Spruce St., Philadelphia.
Executive Secretary-Treasurer: Dr. William P. Wherry, 1500 Medical Arts Bldg., Omaha.
Secretary: Dr. G. L. McCormick, 626 S. Central Ave., Marshfield.

American Ophthalmological Society

President: Dr. Allen Greenwood, 82 Commonwealth Ave., Boston.
Secretary-Treasurer: Dr. Eugene M. Blake, 303 Whitney Ave., New Haven, Conn

Association for Research in Ophthalmology, Inc.

Chairman: Dr. John Evans, 23 Schermerhorn St., Brooklyn.
Secretary-Treasurer: Dr. C. S. O'Brien, University Hospital, Iowa City.

Canadian Medical Association, Section on Ophthalmology

President: Dr. Alexander E. MacDonald, 170 St. George St., Toronto.
Secretary-Treasurer: Dr. L. J. Sebert, 170 St. George St., Toronto.

Canadian Ophthalmological Society

President: Dr. J. Vaillancourt, 46 St. Louis St., Quebec.
Secretary-Treasurer: Dr. Alexander E. MacDonald, 421 Medical Arts Bldg., Toronto.

National Society for the Prevention of Blindness

President: Mr. Mason H. Bigelow, 1790 Broadway, New York.
Secretary: Miss Regina E. Schneider, 1790 Broadway, New York.
Executive Director: Mrs. Eleanor Brown Merrill, 1790 Broadway, New York.

SECTIONAL

Academy of Medicine of Northern New Jersey, Section on Eye, Ear, Nose and Throat

President: Dr. Charles W. Barkhorn, 223 Roseville Ave., Newark.
Secretary: Dr. William F. McKim, 317 Roseville Ave., Newark.
Place: 91 Lincoln Park South, Newark. Time: 8:45 p. m., second Monday of each month, October to May.

Central Wisconsin Society of Ophthalmology and Otolaryngology

President: Dr. D. G. Hugo, 130 Main St., Oshkosh.
Secretary: Dr. G. L. McCormick, 626 S. Central Ave., Marshfield.
Place: Land O'Lakes. Time: June 1942.

NEW ENGLAND OPHTHALMOLOGICAL SOCIETY

President: Dr. William D. Rowland, 84 Commonwealth Ave., Boston.
Secretary-Treasurer: Dr. Trygve Gundersen, 243 Charles St., Boston.
Place: Massachusetts Eye and Ear Infirmary, 243 Charles St., Boston. Time: 8 p. m., third Tuesday of each month from November to April, inclusive.

PACIFIC COAST OTO-OPHTHALMOLOGICAL SOCIETY

President: Dr. Ralph A. Fenton, 1020 S. W. Taylor St., Portland, Ore.
Secretary-Treasurer: Dr. C. Allen Dickey, 450 Sutter St., San Francisco.
Place: Portland, Ore. Time: May 11-14, 1942.

PUGET SOUND ACADEMY OF OPHTHALMOLOGY AND OTO-LARYNGOLOGY

President: Dr. Spencer S. Howe, 103 E. Holly St., Bellingham, Wash.
Secretary-Treasurer: Dr. Barton E. Peden, 419 Stimson Bldg., Seattle.
Place: Seattle or Tacoma, Wash. Time: Third Tuesday of each month, except June, July and August.

ROCK RIVER VALLEY EYE, EAR, NOSE AND THROAT SOCIETY

President: Dr. W. H. Elmer, 321 W. State St., Rockford, Ill.
Secretary-Treasurer: Dr. Harry R. Warner, 321 W. State St., Rockford, Ill.
Place: Rockford, Ill., or Janesville or Beloit, Wis. Time: Third Tuesday of each month from October to April, inclusive.

SAGINAW VALLEY ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President: Dr. M. Kessler, 311 Center Ave., Bay City, Mich.
Secretary-Treasurer: Dr. J. H. Curts, 330 S. Washington Ave., Saginaw, Mich.
Place: Saginaw or Bay City, Mich. Time: Second Tuesday of each month, except July and August.

SIOUX VALLEY EYE AND EAR ACADEMY

President: Dr. J. C. Davis, 1615 Howard St., Omaha.
Secretary-Treasurer: Dr. J. E. Dvorak, 408 Davidson Bldg., Sioux Falls, S. D.

SOUTHERN MEDICAL ASSOCIATION, SECTION ON EYE, EAR, NOSE AND THROAT

Chairman: Dr. L. Chester McHenry, Medical Arts Bldg., Oklahoma City.
Secretary: Dr. J. W. Jervey Jr., 101 Church St., Greenville, S. C.
Place: Richmond, Va. Time: November 1942.

SOUTHWESTERN ACADEMY OF EYE, EAR, NOSE AND THROAT

President: Dr. H. L. Brehmer, 221 W. Central Ave., Albuquerque, N. Mex.
Secretary: Dr. A. E. Cruthirds, 1011 Professional Bldg., Phoenix, Ariz.
Place: Albuquerque, N. Mex. Time: November 1942.

SOUTHWESTERN MICHIGAN TRIOLOGICAL SOCIETY

President: Dr. W. M. Dodge, 716 First National Bank Bldg., Battle Creek.
Secretary-Treasurer: Dr. Kenneth Lowe, 25 W. Michigan Ave., Battle Creek.
Time: Last Thursday of September, October, November, March, April and May.

WESTERN PENNSYLVANIA EYE, EAR, NOSE AND THROAT SOCIETY

President: Dr. C. H. Bailey, 29 S. Oakland Ave., Sharon.
Secretary-Treasurer: Dr. J. McClure Tyson, Deposit Nat'l Bank Bldg., DuBois.

STATE

ARKANSAS STATE MEDICAL SOCIETY, EYE, EAR, NOSE AND THROAT SECTION

President: Dr. R. R. Kirkpatrick, 6th and Walnut Sts., Texarkana, Ark.
Secretary-Treasurer: Dr. Raymond C. Cook, 701 Main St., Little Rock.

COLORADO OPHTHALMOLOGICAL SOCIETY

President: Dr. William M. Bane, 1612 Tremont Pl., Denver.
Secretary: Dr. Harry Shankel, Republic Bldg., Denver.
Place: University Club, Denver. Time: 7:30 p. m., third Saturday of each month, October to May, inclusive.

Connecticut State Medical Society, Section on Eye, Ear, Nose and Throat

President: Dr. Edward N. DeWitt, 836 Myrtle Ave., Bridgeport.
Secretary-Treasurer: Dr. Henry L. Birge, 179 Allyn St., Hartford.

Eye, Ear, Nose and Throat Club of Georgia

President: Dr. E. N. Maner, 247 Bull St., Savannah.
Secretary-Treasurer: Dr. C. K. McLaughlin, 567 Walnut St., Macon.

Indiana Academy of Ophthalmology and Oto-Laryngology

President: Dr. F. McK. Ruby, Union City.
Secretary: Dr. Edwin W. Dyar Jr., 23 E. Ohio St., Indianapolis.
Place: French Lick. Time: First Wednesday in April.

Iowa Academy of Ophthalmology and Oto-Laryngology

President: Dr. J. K. Von Lackum, 117–3d St. S. E., Cedar Rapids.
Secretary-Treasurer: Dr. B. M. Merkel, 604 Locust St., Des Moines.

Louisiana-Mississippi Ophthalmological and Otolaryngological Society

President: Dr. Henry N. Blum, 912 American Bank Bldg., New Orleans.
Secretary-Treasurer: Dr. Edley H. Jones, 1301 Washington St., Vicksburg, Miss.

Michigan State Medical Society, Section of Ophthalmology and Otolaryngology

Chairman: Dr. Robert H. Fraser, 25 W. Michigan Ave., Battle Creek.
Secretary: Dr. R. G. Laird, 114 Fulton St., Grand Rapids.

Minnesota Academy of Ophthalmoloy and Otolaryngology

President: Dr. Erling Wilhelm Hansen, 78 S. 9th St., Minneapolis.
Secretary-Treasurer: Dr. George E. McGeary, 920 Medical Arts Bldg., Minneapolis.
Time: Second Friday of each month from October to May.

Montana Academy of Oto-Ophthalmology

President: Dr. William J. Marshall, 335 Owen St., Missoula.
Secretary: Dr. Fritz D. Hurd, 309 Medical Arts Bldg., Great Falls.

Nebraska Academy of Ophthalmology and Otolaryngology

President: Dr. W. Howard Morrison, 1500 Medical Arts Bldg., Omaha.
Secretary-Treasurer: Dr. John Peterson, 1307 N St., Lincoln.

New Jersey State Medical Society, Section on Ophthalmology, Otology and Rhinolaryngology

Chairman: Dr. Edgar P. Cardwell, 47 Central Ave., Newark.
Secretary: Dr. Arthur E. Sherman, 243 S. Harrison St., East Orange.

New York State Medical Society, Eye, Ear, Nose and Throat Section

Chairman: Dr. Searle B. Marlow, 109 S. Warren St., Syracuse.
Secretary: Dr. C. Stewart Nash, 277 Alexander St., Rochester.

North Carolina Eye, Ear, Nose and Throat Society

President: Dr. M. R. Gibson, Professional Bldg., Raleigh.
Secretary: Dr. Vanderbilt F. Couch, 105 W. 4th St., Winston-Salem.

North Dakota Academy of Ophthalmology and Oto-Laryngology

President: Dr. A. E. Spear, Dickinson.
Secretary-Treasurer: Dr. F. L. Wicks, 516–6th St., Valley City.

OREGON ACADEMY OF OPHTHALMOLOGY AND OTO-LARYNGOLOGY

President: Dr. Paul Bailey, 833 S. W. 11th Ave., Portland.
Secretary-Treasurer: Dr. R. S. Fixott, 1020 S. W. Taylor St., Portland.
Place: Good Samaritan Hospital, Portland. Time: Third Tuesday of each month.

RHODE ISLAND OPHTHALMOLOGICAL AND OTOLOGICAL SOCIETY

Acting President: Dr. N. Darrell Harvey, 112 Waterman St., Providence.
Secretary-Treasurer: Dr. Linley C. Happ, 124 Waterman St., Providence.
Place: Rhode Island Medical Society Library, Providence. Time: 8:30 p. m., second Thursday in October, December, February and April.

SOUTH CAROLINA SOCIETY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President: Dr. J. L. Sanders, 222 N. Main St., Greenville.
Secretary: Dr. J. H. Stokes, 125 W. Cheves St., Florence.
Place: Columbia. Time: November 1942.

TENNESSEE ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President: Dr. Wesley Wilkerson, 700 Church St., Nashville.
Secretary-Treasurer: Dr. W. D. Stinson, 124 Physicians and Surgeons Bldg., Memphis.

TEXAS OPHTHALMOLOGICAL AND OTO-LARYNGOLOGICAL SOCIETY

President: Dr. E. L. Goar, 1300 Walker Ave., Houston.
Secretary: Dr. Dan Brannin, 929 Medical Arts Bldg., Dallas.

UTAH OPHTHALMOLOGICAL SOCIETY

President: Dr. Everett B. Muir, Boston Bldg., Salt Lake City.
Secretary-Treasurer: Dr. Earl H. Phillips, 623 Judge Bldg., Salt Lake City.
Place: University Club, Salt Lake City. Time: 7:00 p. m., third Monday of each month.

VIRGINIA SOCIETY OF OTO-LARYNGOLOGY AND OPHTHALMOLOGY

President: Dr. Mortimer H. Williams, 30½ Franklin Rd. S. W., Roanoke.
Secretary-Treasurer: Dr. Meade Edmunds, 34 Franklin St., Petersburg.

WEST VIRGINIA STATE MEDICAL ASSOCIATION, EYE, EAR, NOSE AND THROAT SECTION

President: Dr. George Traugh, 309 Cleveland Ave., Fairmont.
Secretary: Dr. Welch England, 621½ Market St., Parkersburg.

LOCAL

AKRON ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President: Dr. George E. Ferguson, Second National Bldg., Akron, Ohio.
Secretary-Treasurer: Dr. D. F. Mathias, First Central Tower, Akron, Ohio.
Time: First Monday in January, March, May and November.

ATLANTA EYE, EAR, NOSE AND THROAT SOCIETY

President: Dr. Stacy C. Howell, 144 Ponce de Leon Ave. N. E., Atlanta, Ga.
Secretary: Dr. Lester A. Brown, 478 Peachtree St. N. E., Atlanta, Ga.
Place: Grady Hospital. Time: 6:00 p. m., second Wednesday of each month from October to May.

BALTIMORE MEDICAL SOCIETY, SECTION ON OPHTHALMOLOGY

Chairman: Dr. Ernst Bodenheimer, 1212 Eutaw Pl., Baltimore.
Secretary: Dr. Thomas R. O'Rourk, 104 W. Madison St., Baltimore.
Place: Medical and Chirurgical Faculty, 1211 Cathedral St. Time: 8:30 p. m. fourth Thursday of each month from October to March.

Birmingham Eye, Ear, Nose and Throat Club

President: Each member, in alphabetical order.
Secretary: Dr. Luther E. Wilson, 919 Woodward Bldg., Birmingham, Ala.
Place: Tutwiler Hotel. Time: 6:30 p. m., second Tuesday of each month, September to May, inclusive.

Brooklyn Ophthalmological Society

President: Dr. Maurice Wieselthier, 1322 Union St., Brooklyn.
Secretary-Treasurer: Dr. Harold F. Schilback, 142 Joralemon St., Brooklyn.
Place: Kings County Medical Society Bldg., 1313 Bedford Ave. Time: Third Thursday in February, April, May, October and December.

Buffalo Ophthalmologic Club

President: Dr. Meyer H. Riwchun, 367 Linwood Ave., Buffalo.
Secretary-Treasurer: Dr. Sheldon B. Freeman, 196 Linwood Ave., Buffalo.
Time: Second Thursday of each month.

Chattanooga Society of Ophthalmology and Otolaryngology

President: Each member, in alphabetical order.
Secretary: Dr. Douglas Chamberlain, Chattanooga Bank Bldg., Chattanooga, Tenn.
Place: Mountain City Club. Time: Second Thursday of each month from September to May.

Chicago Ophthalmological Society

President: Dr. Sanford Gifford, 720 N. Michigan Ave., Chicago.
Secretary-Treasurer: Dr. Vernon M. Leech, 55 E. Washington St., Chicago.
Place: Chicago Towers Club, 505 N. Michigan Ave. Time: Third Monday of each month from October to May.

Cincinnati General Hospital Ophthalmology Staff

Chairman: Dr. D. T. Vail, 441 Vine St., Cincinnati.
Secretary: Dr. A. A. Levin, 441 Vine St., Cincinnati.
Place: Cincinnati General Hospital. Time: 7:45 p. m., third Friday of each month except June, July and August.

Cleveland Ophthalmological Club

Chairman: Dr. W. J. Abbott, 10515 Carnegie Ave., Cleveland.
Secretary: Dr. L. V. Johnson, 2065 Adelbert Rd., Cleveland.
Time: Second Tuesday in October, December, February and April.

College of Physicians, Philadelphia, Section on Ophthalmology

Chairman: Dr. Francis H. Adler, 313 S. 17th St., Philadelphia.
Clerk: Dr. W. S. Reese, 1901 Walnut St., Philadelphia.
Time: Third Thursday of every month from October to April, inclusive.

Columbus Ophthalmological and Oto-Laryngological Society

Chairman: Dr. C. D. Postle, 240 E. State St., Columbus, Ohio.
Secretary-Treasurer: Dr. Hugh C. Thompson, 289 E. State St., Columbus, Ohio.
Place: The Neil House. Time: 6 p. m., first Monday of each month.

Corpus Christi Eye, Ear, Nose and Throat Society

Chairman: Dr. F. K. Stroud, 416 Chaparral St., Corpus Christi, Texas.
Secretary: Dr. Arthur Padilla, 414 Medical Professional Bldg., Corpus Christi, Texas.
Time: Second Friday of each month from October to May.

Dallas Academy of Ophthalmology and Oto-Laryngology

President: Dr. L. A. Nelson, 4105 Live Oak St., Dallas, Texas.
Secretary: Dr. S. F. Harrington, 921 Medical Arts Bldg., Dallas, Texas.
Place: Dallas Athletic Club. Time: 6:30 p. m., first Tuesday of each month from October to June. The November, January and March meetings are devoted to clinical work.

Des Moines Academy of Ophthalmology and Otolaryngology

President: Dr. H. C. Schmitz, 604 Locust St., Des Moines, Iowa.
Secretary-Treasurer: Dr. Byron M. Merkel, 604 Locust St., Des Moines, Iowa.
Time: 7:45 p. m., third Monday of every month from September to May.

Detroit Ophthalmological Club

Chairman: Members rotate alphabetically.
Secretary: Dr. Harvey E. Dowling, 2414 Eaton Tower, Detroit.
Time: 6:30 p. m., first Wednesday of each month.

Detroit Ophthalmological Society

President: Dr. Parker Heath, 1553 Woodward Ave., Detroit.
Secretary: Dr. Leland F. Carter, 1553 Woodward Ave., Detroit.
Place: Club rooms of Wayne County Medical Society. Time: Third Thursday of each month from November to April, inclusive.

Eastern New York Eye, Ear, Nose and Throat Association

President: Dr. James M. Dunn, 1352 Union St., Schenectady.
Secretary-Treasurer: Dr. Joseph L. Holohan, 330 State St., Albany.
Time: Third Wednesday in October, November, March, April, May and June.

Fort Worth Eye, Ear, Nose and Throat Society

President: Dr. W. R. Thompson, 602 W. 10th St., Fort Worth, Texas.
Secretary-Treasurer: Dr. A. E. Jackson, 602 W. 10th St., Fort Worth, Texas.
Place: Medical Hall, Medical Arts Bldg. Time: 7:30 p. m., first Friday of each month except July and August.

Houston Academy of Medicine, Ophthalmological and Oto-Laryngological Section

President: Dr. Felician J. Slataper, 1110-1111 Medical Arts Bldg., Houston, Texas.
Secretary: Dr. Theo. L. Holland, 611 Medical Arts Bldg., Houston, Texas.
Place: Medical Arts Bldg., Harris County Medical Society Rooms. Time: 8 p. m., second Thursday of each month from September to June.

Indianapolis Ophthalmological and Otolaryngological Society

President: Dr. John I. Garret, 57 Stokes Bldg., Indianapolis.
Secretary: Dr. Kenneth L. Craft, 23 E. Ohio St., Indianapolis.
Place: Indianapolis Athletic Club. Time: 6:30 p. m., second Thursday of each month from November to May.

Kansas City Society of Ophthalmology and Oto-Laryngology

President: Dr. Homer Beal, 1103 Grand Ave., Kansas City, Mo.
Secretary: Dr. Desmond Curran, Federal Reserve Bank Bldg., Kansas City, Mo.
Time: Third Thursday of each month from October to June. The November, January and March meetings are devoted to clinical work.

Long Beach Eye, Ear, Nose and Throat Society

Chairman: Dr. Harold Snow, 614 S. Pacific Ave., San Pedro, Calif.
Secretary-Treasurer: Dr. Oliver R. Nees, 508 Times Bldg., Long Beach, Calif.
Place: Professional Bldg. Time: Last Wednesday of each month from October to May.

Los Angeles Society of Ophthalmology and Otolaryngology

President: Dr. John Osburn, 523 W. 6th St., Los Angeles.
Secretary-Treasurer: Dr. Colby Hall, 1136 W. 6th St., Los Angeles.
Place: Los Angeles County Medical Association Bldg., 1925 Wilshire Blvd. Time: 6:00 p. m., fourth Monday of each month from September to May, inclusive.

Louisville Eye and Ear Society

President: Dr. Joseph S. Heitger, Heyburn Bldg., Louisville, Ky.
Secretary-Treasurer: Dr. J. W. Fish, 321 W. Broadway, Louisville, Ky.
Place: Brown Hotel. Time: 6:30 p. m., second Thursday of each month from September to May, inclusive.

Lower Anthracite Eye, Ear, Nose and Throat Society

Chairman: Each member in alphabetical order.
Secretary: Dr. James J. Monohan, 31 S. Jardin St., Shenendoah, Pa.

Medical Society of the District of Columbia, Section of Ophthalmology and Otolaryngology

Chairman: Dr. E. J. Cummings, 1835 I St. N. W., Washington.
Secretary: Dr. P. S. Constantinople, 1835 I St. N. W., Washington.
Place: 1718 M St. N. W. Time: 8 p. m., third Friday of each month from October to April, inclusive.

Memphis Society of Ophthalmology and Otolaryngology

Chairman: Each member, in alphabetical order.
Secretary: Dr. Sam H. Sanders, 1089 Madison Ave., Memphis, Tenn.
Place: Eye Clinic of Memphis Eye, Ear, Nose and Throat Hospital. Time: 8 p. m., second Tuesday of each month from September to May.

Milwaukee Oto-Ophthalmic Society

President: Dr. John W. Truitt, 161 W. Wisconsin Ave., Milwaukee.
Secretary-Treasurer: Dr. Ralph T. Rank, 238 W. Wisconsin Ave., Milwaukee.
Place: University Club. Time: 6:30 p. m., second Tuesday of each month.

Montgomery County Medical Society

Chairman: Dr. H. V. Dutrow, 1040 Fidelity Medical Bldg., Dayton, Ohio.
Secretary-Treasurer: Dr. Maitland D. Place, 981 Reibold Bldg., Dayton, Ohio.
Place: Van Cleve Hotel. Time: 6:30 p. m., first Tuesday of each month from October to June, inclusive.

Montreal Ophthalmological Society

President: Dr. J. Rosenbaum, 1396 Ste. Catherine St. W., Montreal, Canada.
Secretary: Dr. L. Tessier, 1230 St. Joseph Blvd. E., Montreal, Canada.
Time: Second Thursday of October, December, February and April.

Nashville Academy of Ophthalmology and Otolaryngology

Chairman: Dr. Andrew Hollabaugh, Doctors Bldg., Nashville, Tenn.
Secretary: Dr. Guy Maness, Medical Arts Bldg., Nashville, Tenn.
Place: St. Thomas Hospital. Time: 8 p. m., third Monday of each month from October to May.

New Haven Ophthalmological Society

President: Dr. William H. Ryder, 185 Church St., New Haven, Conn.
Secretary: Dr. Frederick A. Wies, 255 Bradley St., New Haven, Conn.

New Orleans Ophthalmological and Otolaryngological Society

President: Dr. W. B. Clark, 1012 American Bank Bldg., New Orleans.
Secretary: Dr. Mercer G. Lynch, 1018 Maison Blanche Bldg., New Orleans.
Place: Louisiana State University Medical Bldg. Time: 8 p. m., second Tuesday of each month from October to May.

NEW YORK ACADEMY OF MEDICINE, SECTION OF OPHTHALMOLOGY

Chairman: Dr. Kaufman Schlivek, 1016–5th Ave., New York.
Secretary: Dr. Brittain Payne, 896 Madison Ave., New York.
Time: 8:30 p. m., third Monday of every month from October to May, inclusive.

NEW YORK SOCIETY FOR CLINICAL OPHTHALMOLOGY

President: Dr. James W. Smith, 1016–5th Ave., New York.
Secretary: Dr. Benjamin Esterman, 983 Park Ave., New York.
Place: Squibb Hall, 745–5th Ave. Time: 8 p. m., first Monday of each month from October to May, inclusive.

OKLAHOMA CITY ACADEMY OF OPHTHALMOLOGY AND OTOLARYNGOLOGY

President: Dr. R. E. Leatherock, Cushing, Okla.
Secretary: Dr. Harry C. Ford, 1014 Medical Arts Bldg., Oklahoma City.
Place: University Hospital. Time: Second Tuesday of each month from September to May.

OMAHA AND COUNCIL BLUFFS OPHTHALMOLOGICAL AND OTO-LARYNGOLOGICAL SOCIETY

President: Dr. Harold Gifford, 1620 Medical Arts Bldg., Omaha.
Secretary-Treasurer: Dr. W. Howard Morrison, 1500 Medical Arts Bldg., Omaha.
Place: Omaha Club, 20th and Douglas Sts., Omaha. Time: 6 p. m., dinner; 7 p. m., program; third Wednesday of each month from October to May.

PASSAIC-BERGEN OPHTHALMOLOGICAL CLUB

President: Dr. L. Markowitz, 16 Church St., Paterson, N. J.
Secretary-Treasurer: Dr. A. John Reinhorn, 302 Broadway, Paterson, N. J.
Place: Paterson Eye and Ear Infirmary. Time: 9 p. m., last Friday of every month, except June, July and August.

PHILADELPHIA COUNTY MEDICAL SOCIETY, EYE SECTION

Chairman: Dr. Edmund B. Spaeth, 1930 Chestnut St., Philadelphia.
Secretary: Dr. Wilfred E. Fry, 1819 Chestnut St., Philadelphia.
Time: First Thursday of each month from October to May.

PITTSBURGH OPHTHALMOLOGICAL SOCIETY

President: Dr. J. Clyde Markel, 200–9th St., Pittsburgh.
Secretary: Dr. George H. Shuman, 351–5th Ave., Pittsburgh.
Place: Pittsburgh Academy of Medicine Bldg. Time: Fourth Monday of each month, except June, July, August and September.

READING EYE, EAR, NOSE AND THROAT SOCIETY

President: Dr. James E. Landis, 232 N. 6th St., Reading, Pa.
Secretary: Dr. Paul C. Craig, 232 N. 5th St., Reading, Pa.
Place: Wyomissing Club. Time: 6:30 p. m., third Wednesday of each month from October to July.

RICHMOND OPHTHALMOLOGICAL AND OTO-LARYNGOLOGICAL SOCIETY

President: Dr. W. F. Bryce, Medical Arts Bldg., Richmond, Va.
Secretary: Dr. Richard W. Vaughan, Medical Arts Bldg., Richmond, Va.
Place: Westmoreland Club. Time: 6 p. m., second Monday of each month from October to May.

ROCHESTER EYE, EAR, NOSE AND THROAT SOCIETY

President: Dr. E. J. Avery, 11 N. Goodman St., Rochester, N. Y.
Secretary-Treasurer: Dr. Charles T. Sullivan, 277 Alexander St., Rochester, N. Y.

St. Louis Ophthalmic Society

President: Dr. William M. James, 508 N. Grand Blvd., St. Louis.
Secretary: Dr. H. Rommel Hildreth, 823 Metropolitan Bldg., St. Louis.
Place: Oscar Johnson Institute. Time: Clinical meeting 5:30 p. m., dinner and scientific meeting 6:30 p. m., fourth Friday of each month from October to April, inclusive, except December.

San Antonio Ophthalmo-Oto-Laryngological Society

President: Dr. Dan Russell, 705 E. Houston St., San Antonio, Texas.
Secretary-Treasurer: Dr. P. G. Bowen, 315 Camden St., San Antonio, Texas.
Place: Bexar County Medical Library. Time: 8 p. m., first Tuesday of each month from October to May.

San Francisco County Medical Society, Section on Eye, Ear, Nose and Throat

Chairman: Dr. Fred Boyle, 490 Post St., San Francisco.
Secretary: Dr. Frank Hand, 450 Sutter St., San Francisco.
Place: Society's Bldg., 2180 Washington St., San Francisco. Time: Fourth Tuesday of every month except June, July and December.

Shreveport Eye, Ear, Nose and Throat Society

President: Dr. David C. Swearingen, Slattery Bldg., Shreveport, La.
Secretary-Treasurer: Dr. Kenneth Jones, Medical Arts Bldg., Shreveport, La.
Place: Shreveport Charity Hospital. Time: 7:30 p. m., first Monday of every month except July, August and September.

Spokane Academy of Ophthalmology and Oto-Laryngology

President: Dr. Louis A. Parsell, 407 Riverside Ave., Spokane, Wash.
Secretary: Dr. Robert L. Pohl, 407 Riverside Ave., Spokane, Wash.
Place: Paulsen Medical and Dental Library. Time: 8 p. m., fourth Tuesday of each month except June, July and August.

Syracuse Eye, Ear, Nose and Throat Society

President: Dr. Roy Seeley Moore, 1704 State Tower Bldg., Syracuse, N. Y.
Secretary-Treasurer: Dr. I. H. Blaisdell, 713 E. Genesee St., Syracuse, N. Y.
Place: University Club. Time: First Tuesday of each month except June, July and August.

Toledo Eye, Ear, Nose and Throat Society

Chairman: Dr. John D. Skow, 2001 Collingwood Blvd., Toledo, Ohio.
Secretary: Dr. S. H. Patterson, 125–15th Ave., Toledo, Ohio.
Place: Toledo Club. Time: Each month except June, July and August.

Toronto Academy of Medicine, Section of Ophthalmology

Chairman: Dr. W. R. F. Luke, 316 Medical Arts Bldg., Toronto, Canada.
Secretary: Dr. W. T. Gratton, 216 Medical Arts Bldg., Toronto, Canada.
Place: Academy of Medicine, 13 Queens Park. Time: First Monday of each month, November to April.

Washington, D. C., Ophthalmological Society

President: Dr. E. Leonard Goodman, 1801 I St. N. W., Washington, D. C.
Secretary-Treasurer: Dr. Sterling Bockoven, 1752 Massachusetts Ave. N. W., Washington, D. C.
Place: Episcopal Eye, Ear and Throat Hospital. Time: 7:30 p. m., first Monday in November, January, March and April.

Wilkes-Barre Ophthalmological Society

Chairman: Each member in turn.
Secretary: Dr. Samuel T. Buckman, 70 S. Franklin St., Wilkes-Barre, Pa.
Place: Office of chairman. Time: Last Tuesday of each month from October to May.